

Figure 1A. Introduction of orthoester modifications to the sense strand of siRNA duplex results in a functional entity, 24 hour time point.

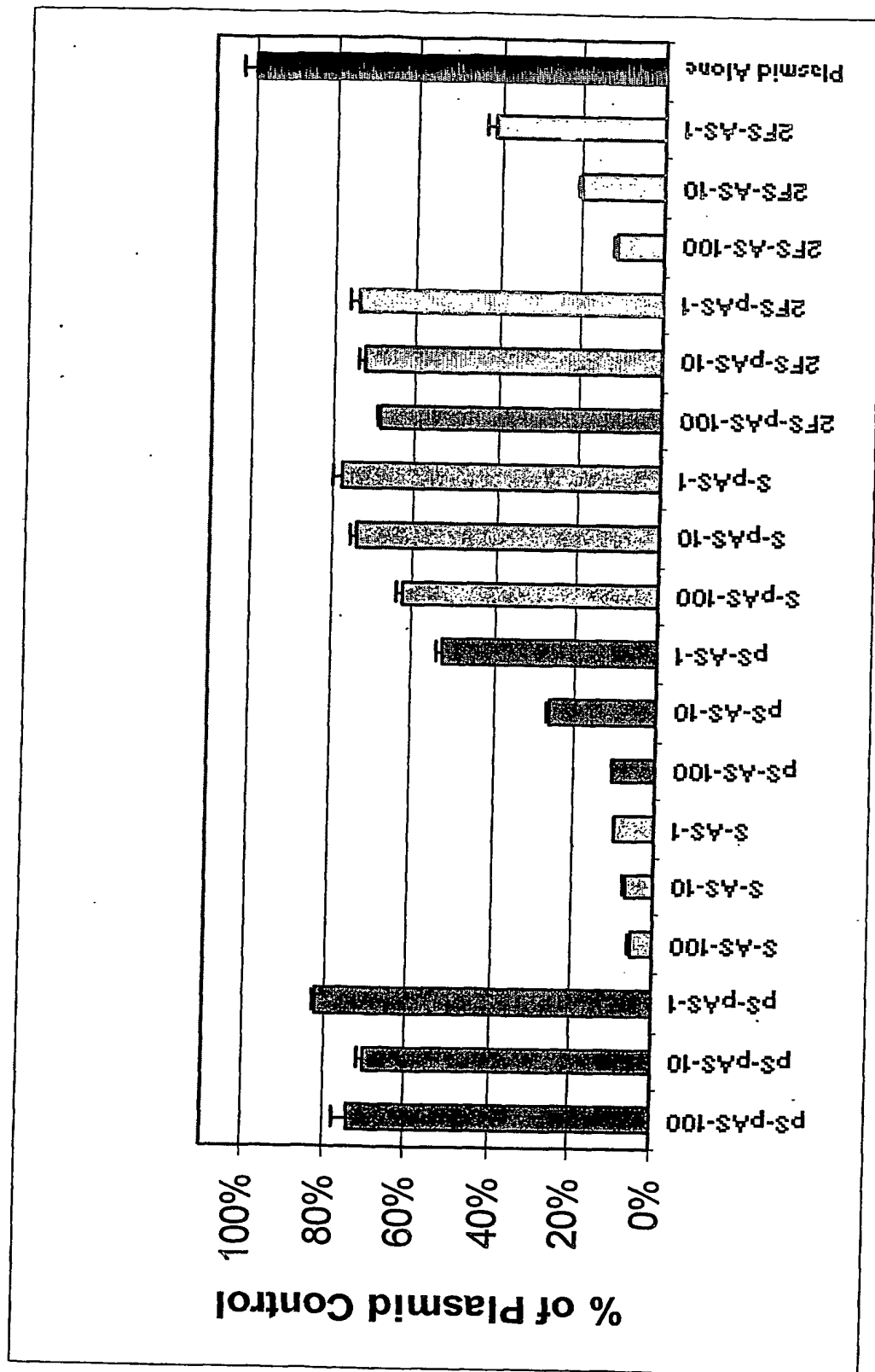
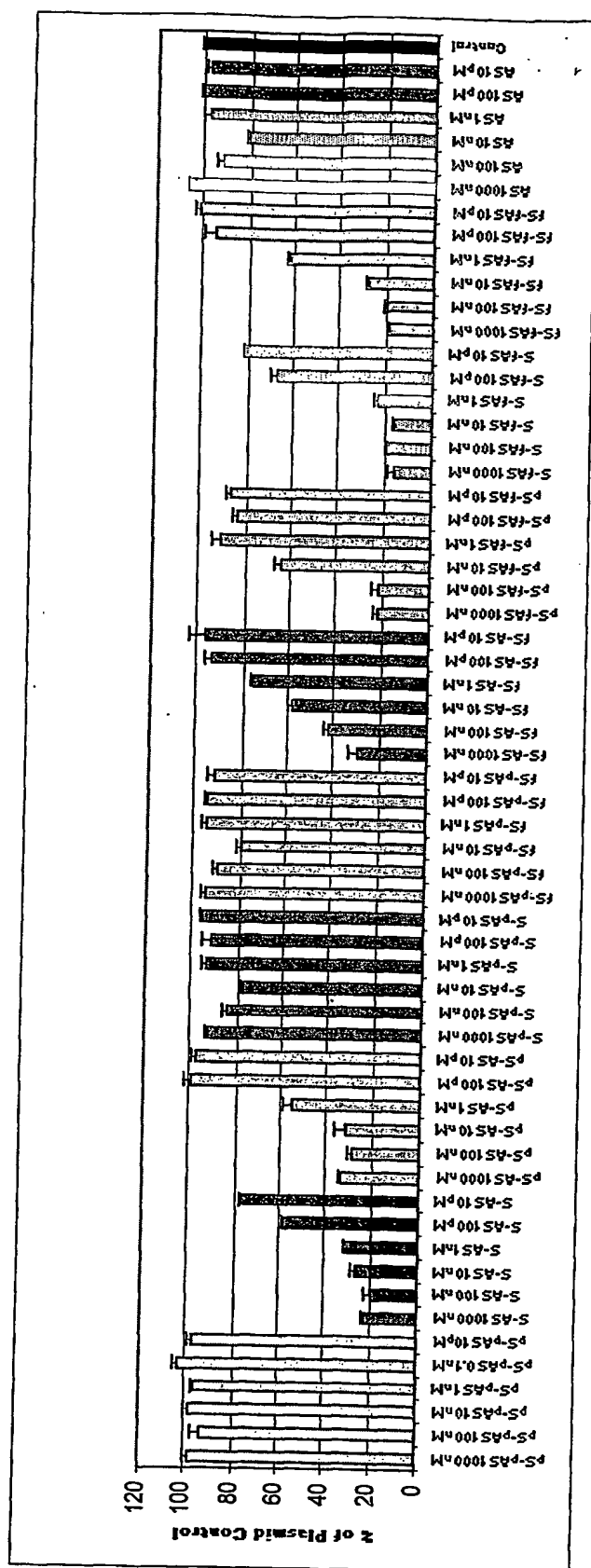
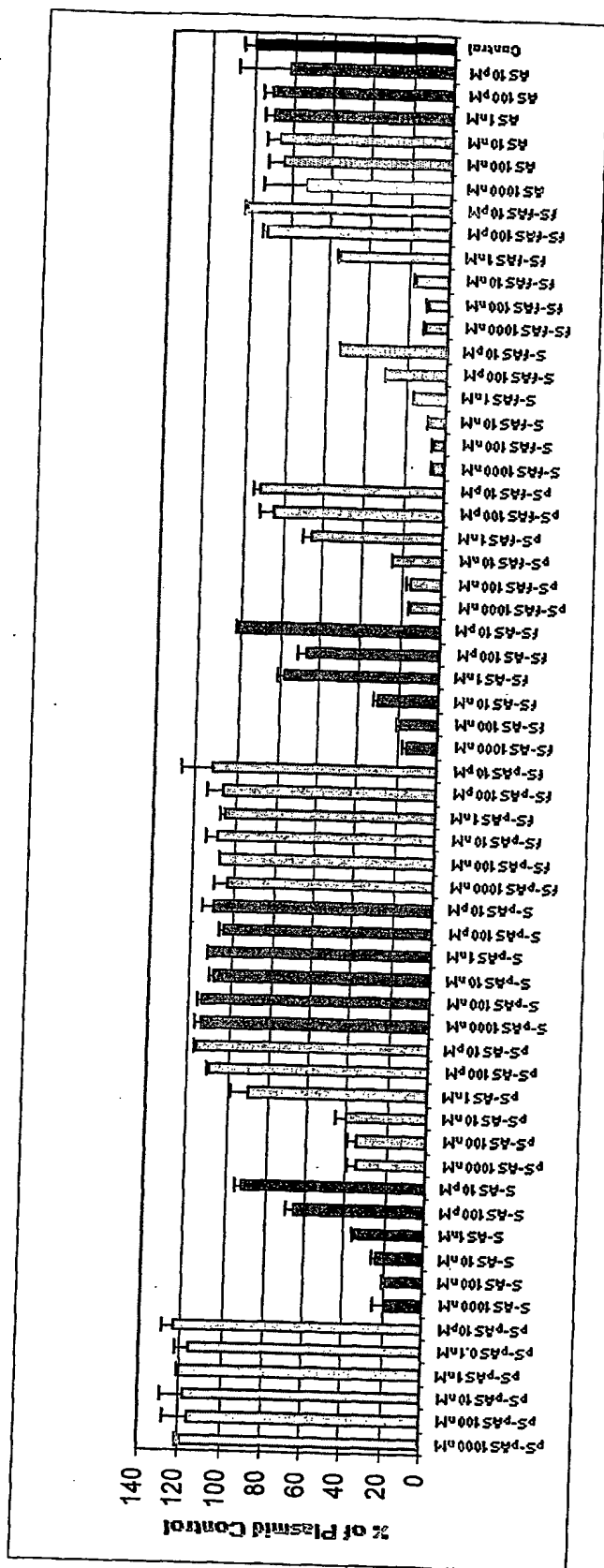


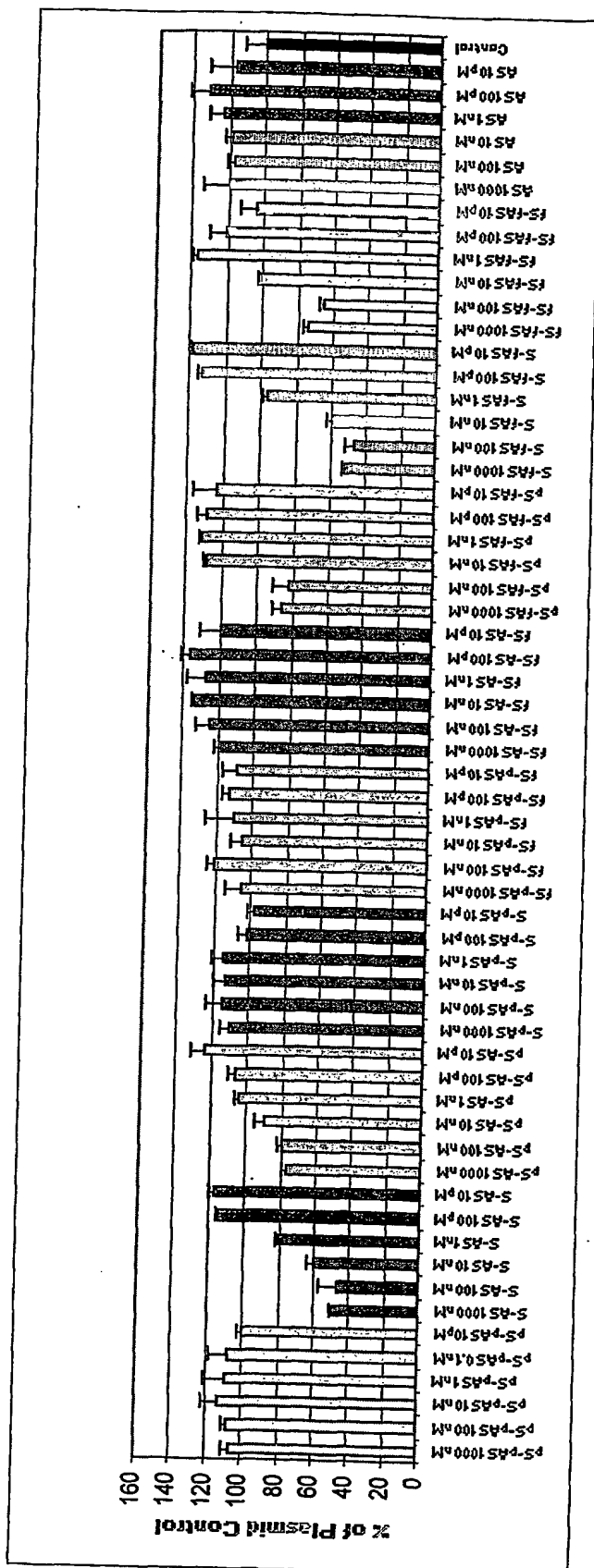
Figure 1B. Introduction of orthoester modifications to the sense strand of an siRNA duplex results in a functional entity, 48 hour time point.



**Figure 2A. Time course of orthoester and 2'F modified siRNAs in cell culture, 24 hour time point.**



**Figure 2B. Time course of orthoester and 2'F modified siRNAs in cell culture, 72 hour time point.**



**Figure 2C. Time course of orthoester and 2'F modified siRNAs in cell culture, 144 hour time point.**

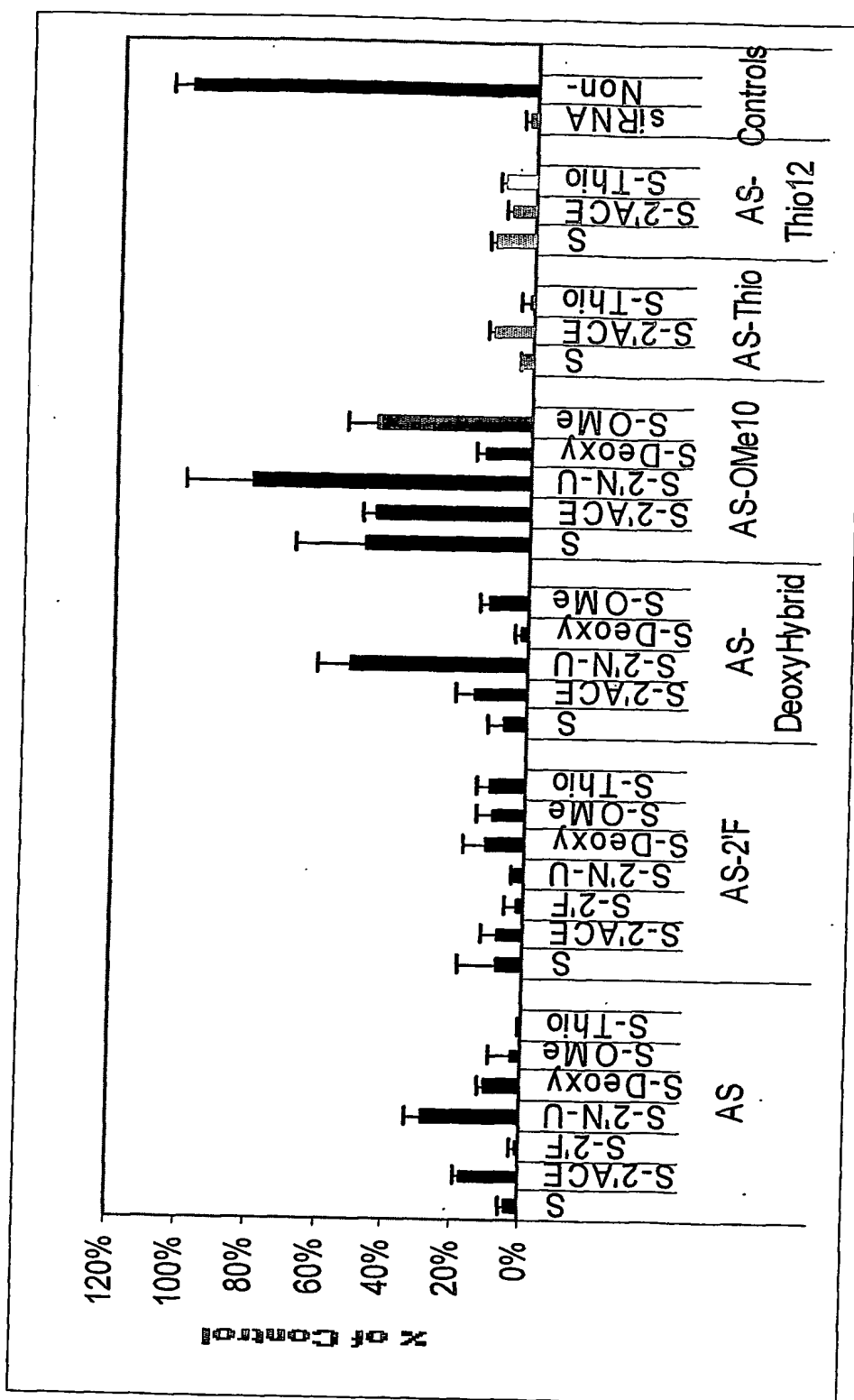


Figure 3. Modifications tolerance in siRNA: sense screen.

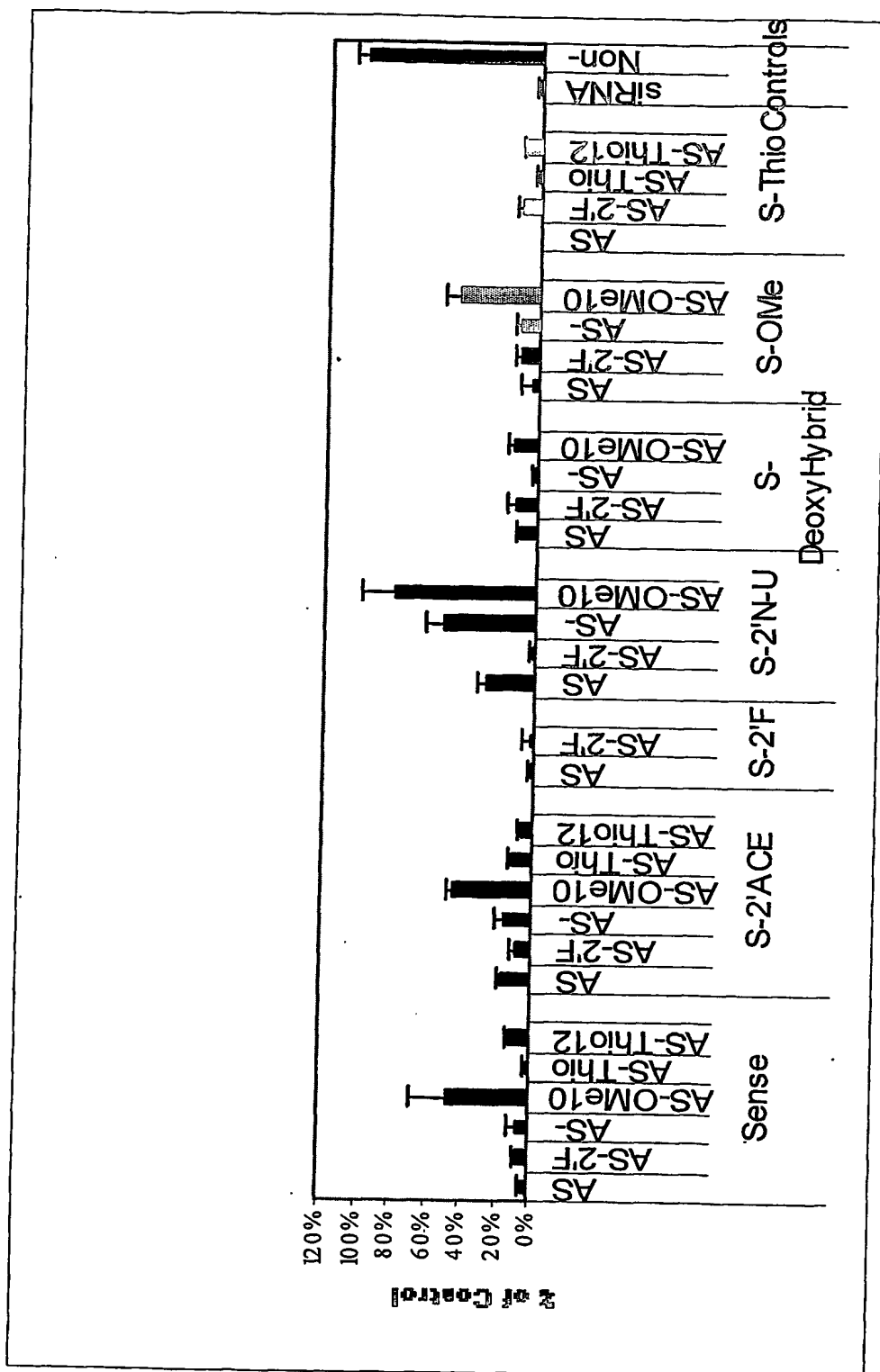


Figure 4. Modifications tolerance in siRNA: antisense screen.

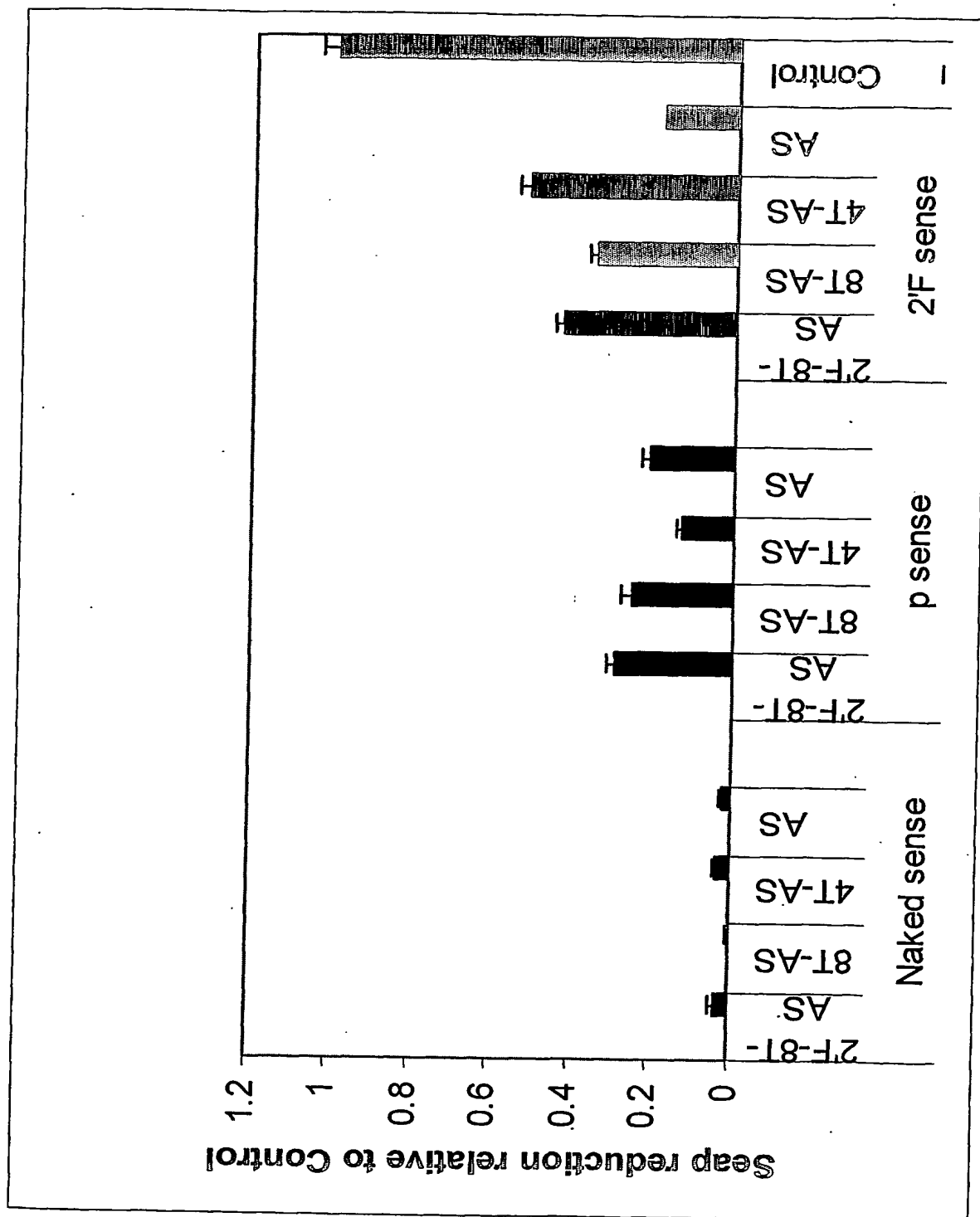


Figure 5. Thio-Based Modifications on the antisense strand



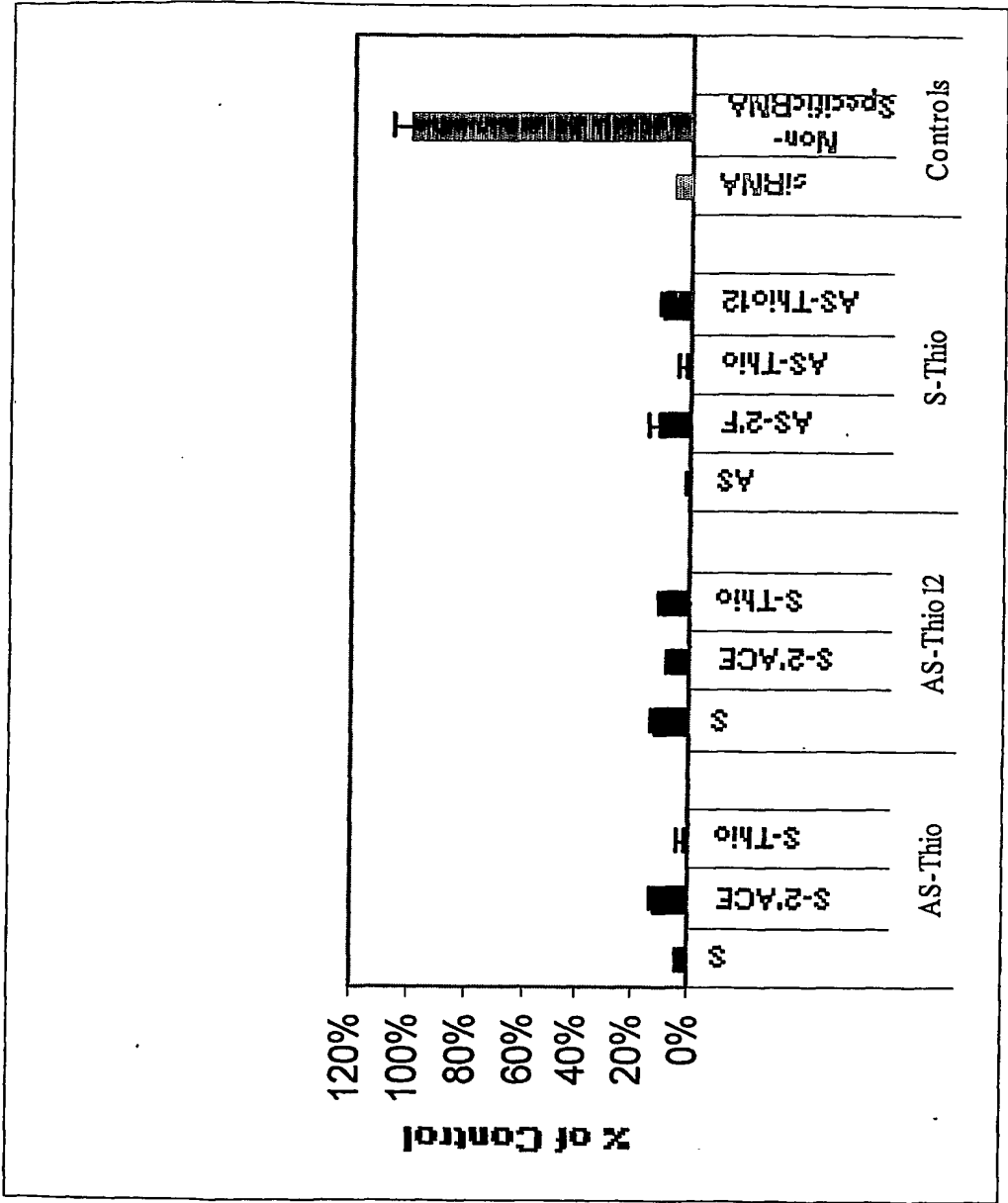


Figure 6. Phosphorothioate modifications are tolerable in both sense and antisense strands

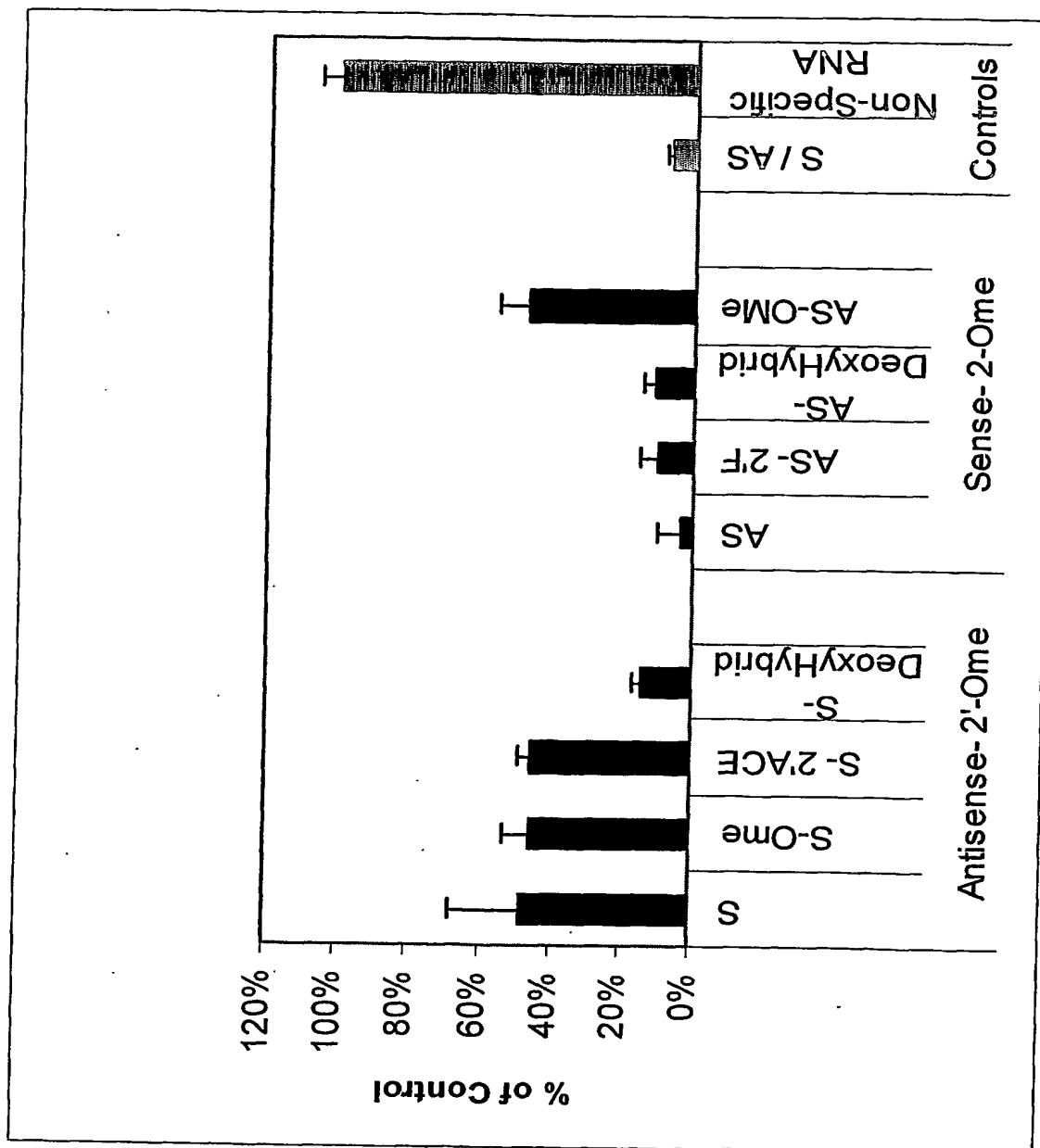


Figure 7. 2'-O-Methyl modifications in RNA interference.

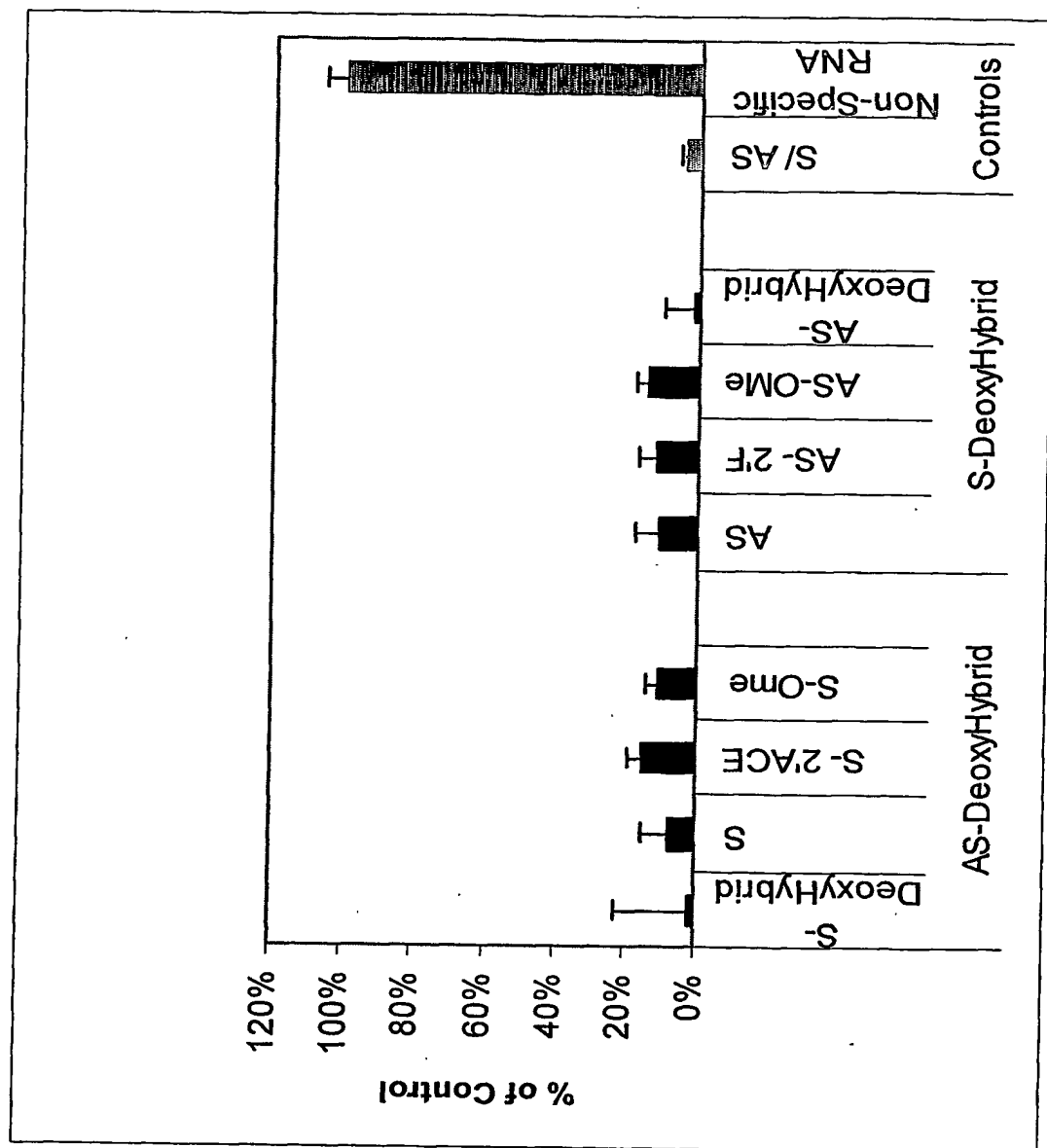
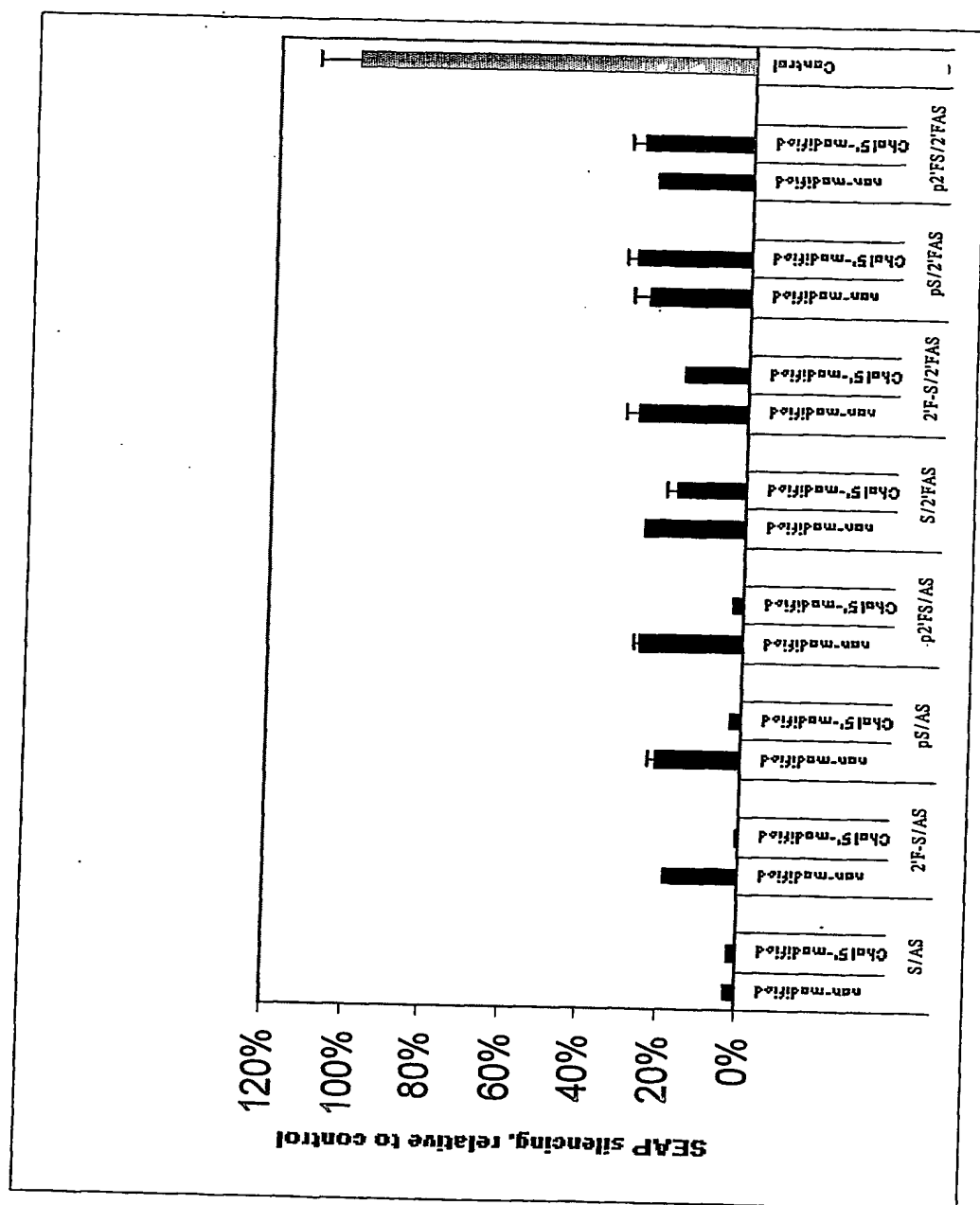


Figure 8. 2'Deoxy-ribo hybrids in RNA interference



**Figure 9. A cholesterol conjugate on the 5' end of the sense strand of an siRNA duplex increases potency of modified siRNA**

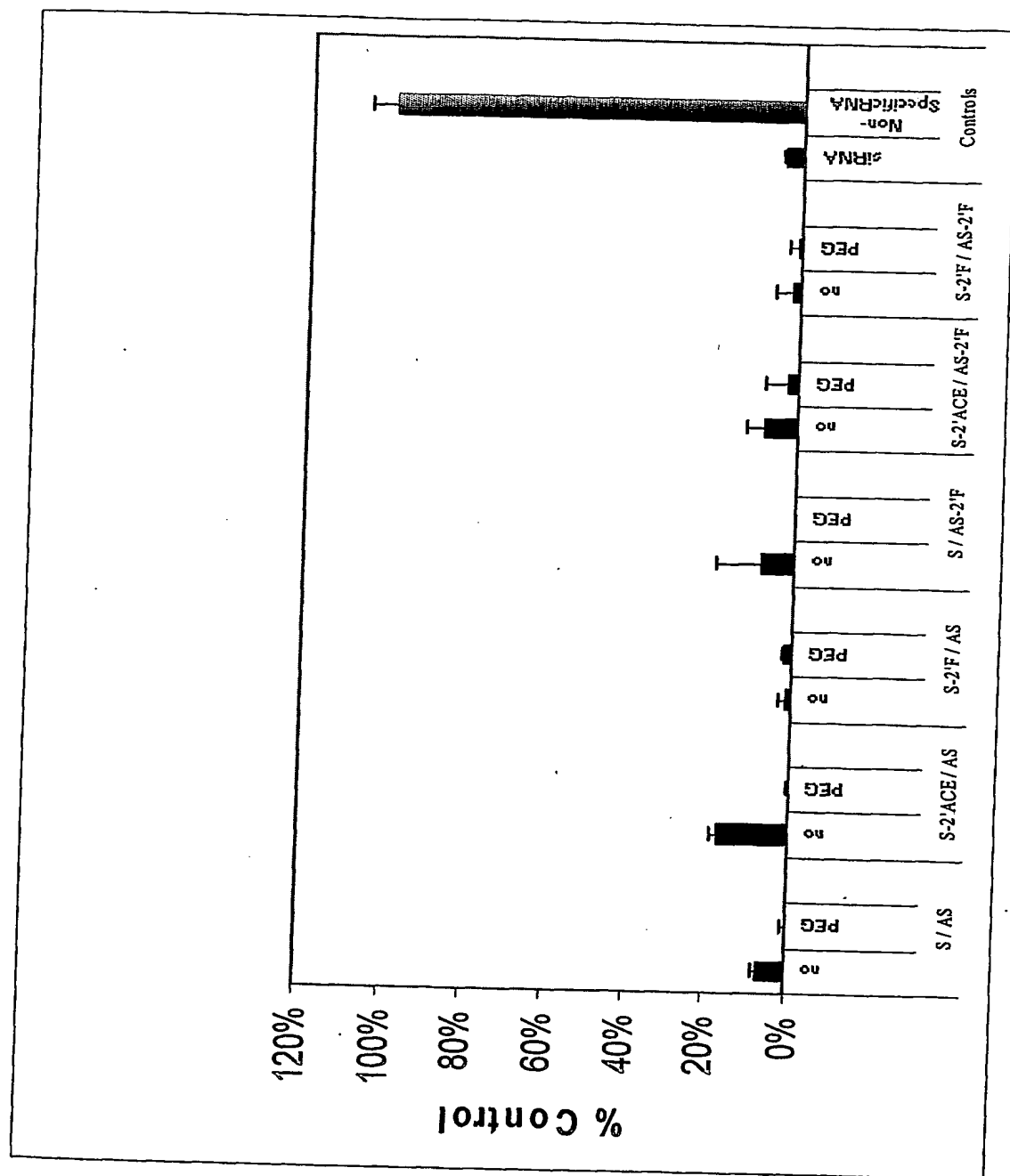


Figure 10. A PEG conjugate on the 5' end of the sense strand of an siRNA duplex increases siRNA potency

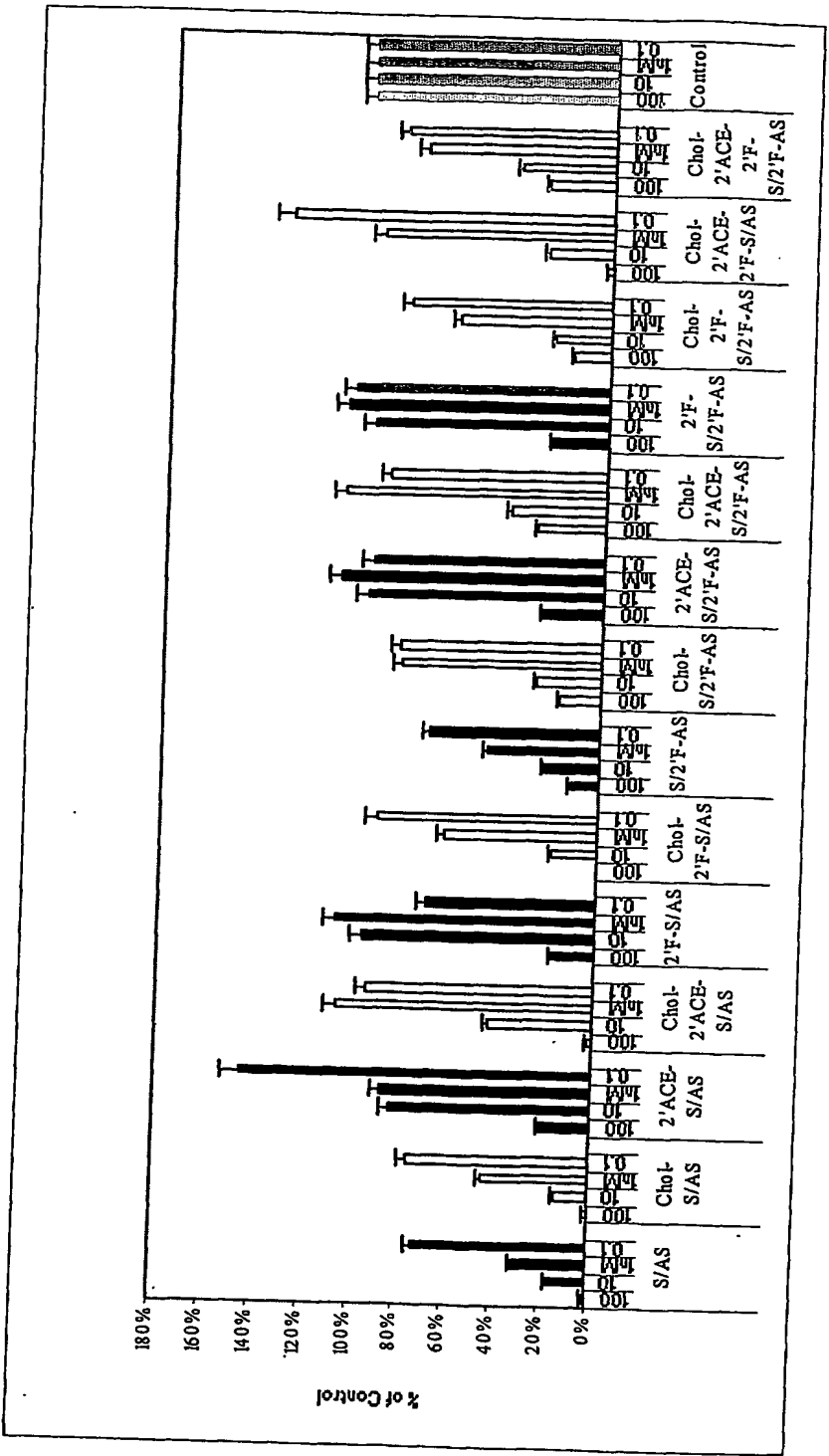
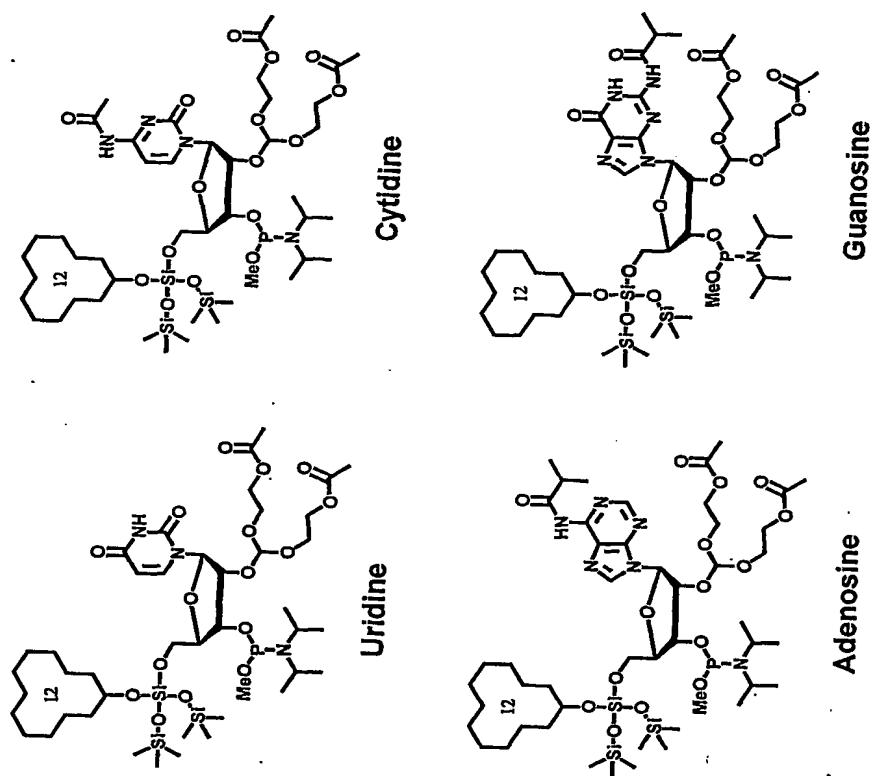


Figure 11. A sense strand having a 5' cholesterol conjugate results in increased potency and decreased dose of 2'F and orthoester modified oligos



**Figure 12: Protected RNA nucleoside phosphoramidites for Dharmacon 2'-ACE RNA synthesis chemistry.**

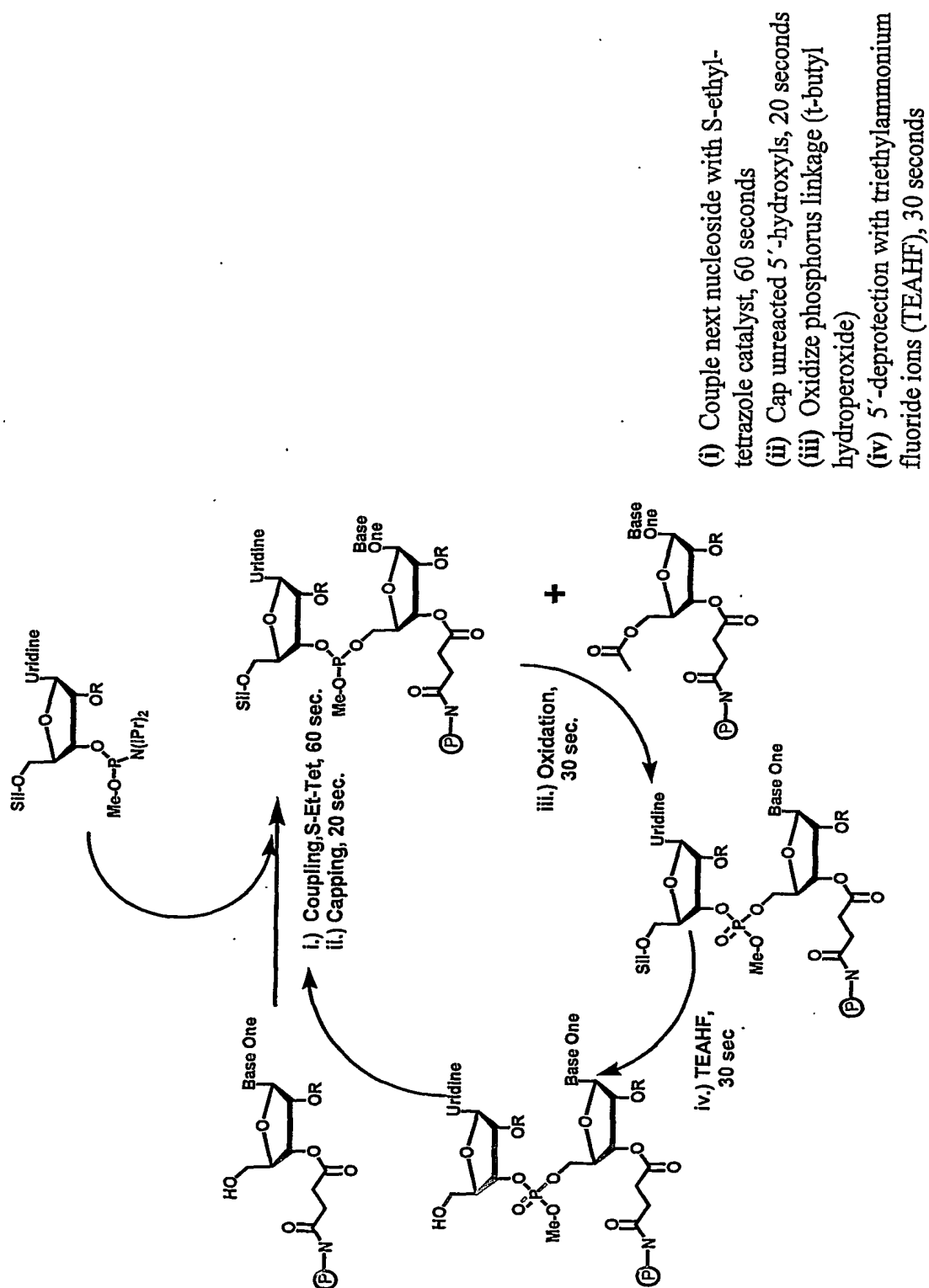


Figure 13: Outline of Dharmacon RNA Synthesis Cycle.



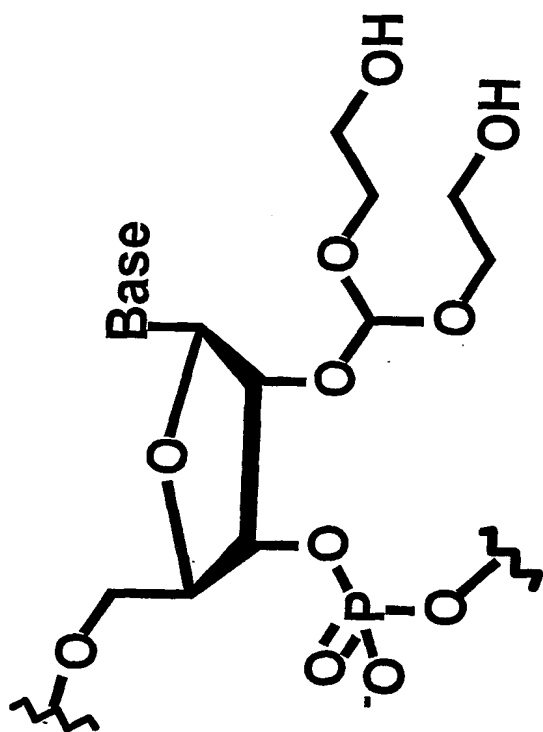


Figure 14: Structure of 2'-ACE protected RNA.

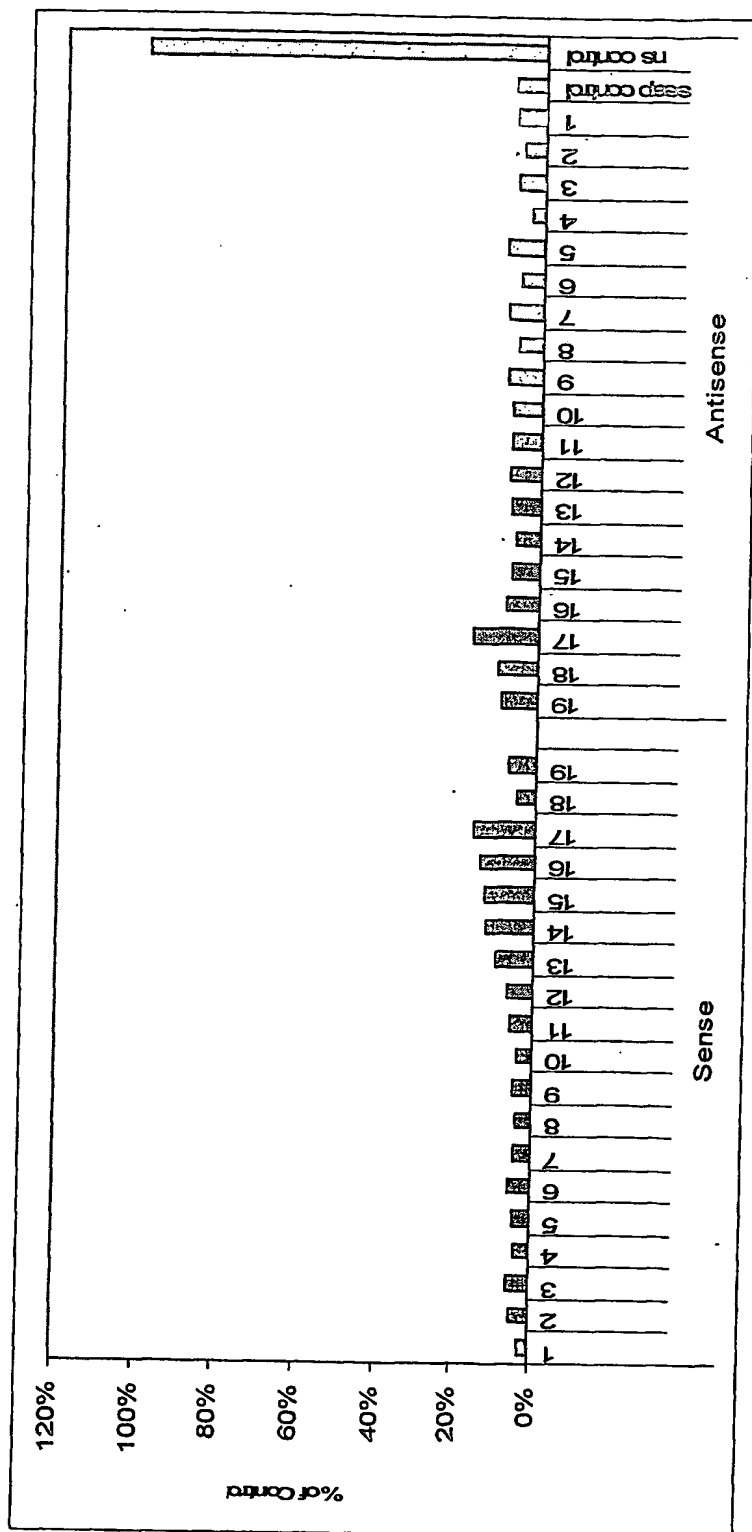


Figure 15A: Single Deoxynucleotide Modification

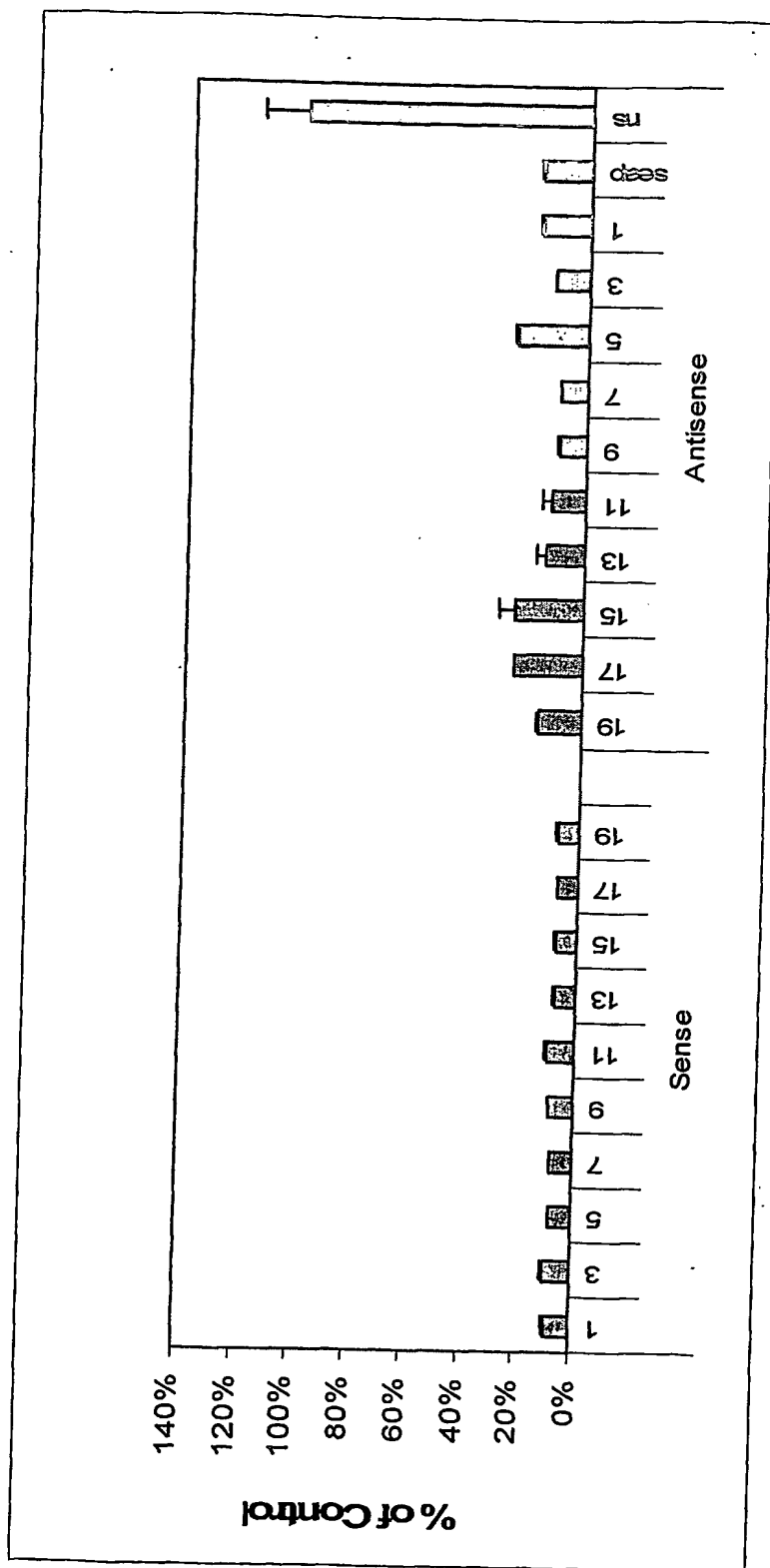


Figure 15B: Two Deoxynucleotide Modifications in Tandem

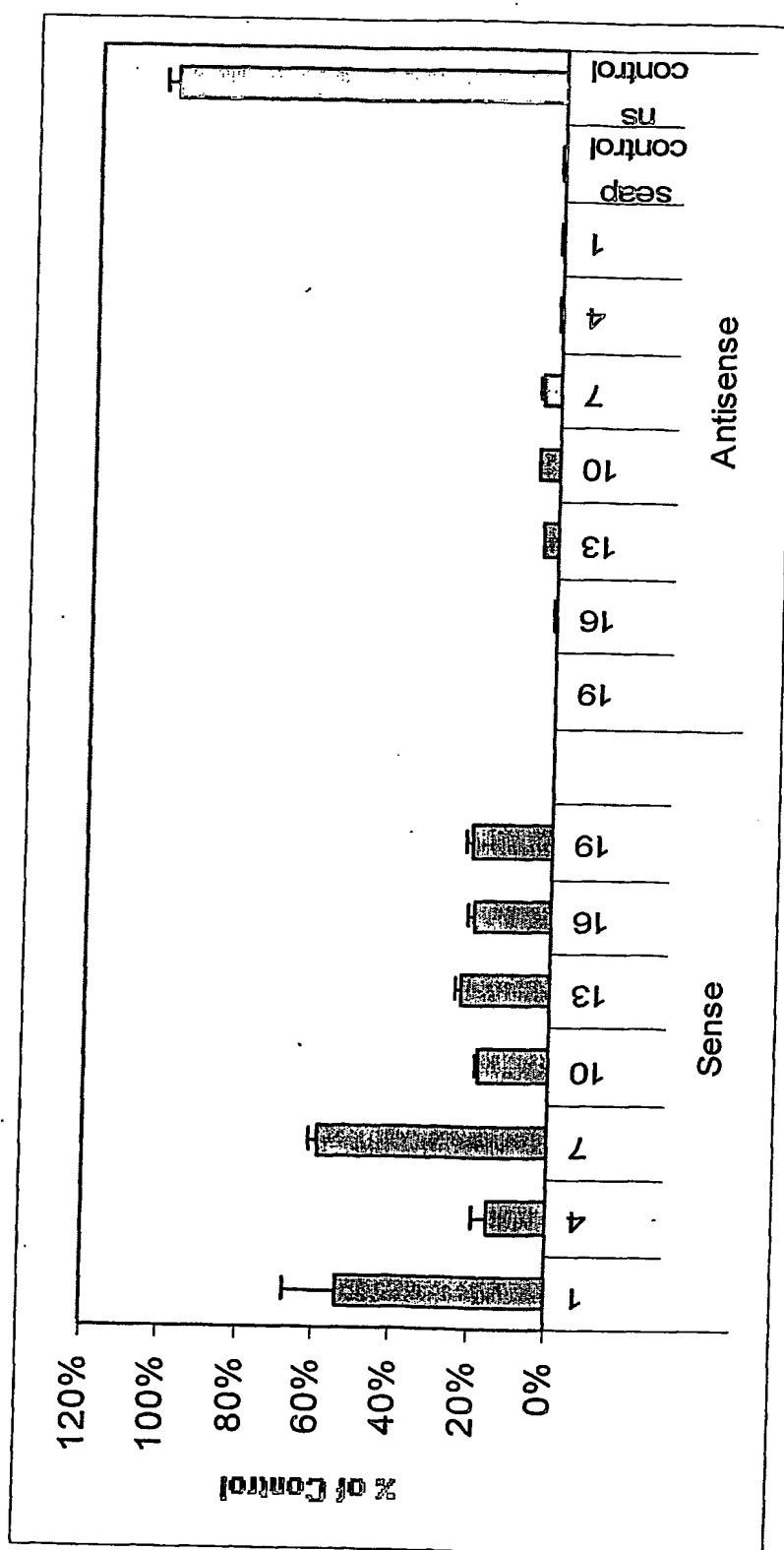


Figure 15C: Three Deoxynucleotide Modifications in Tandem

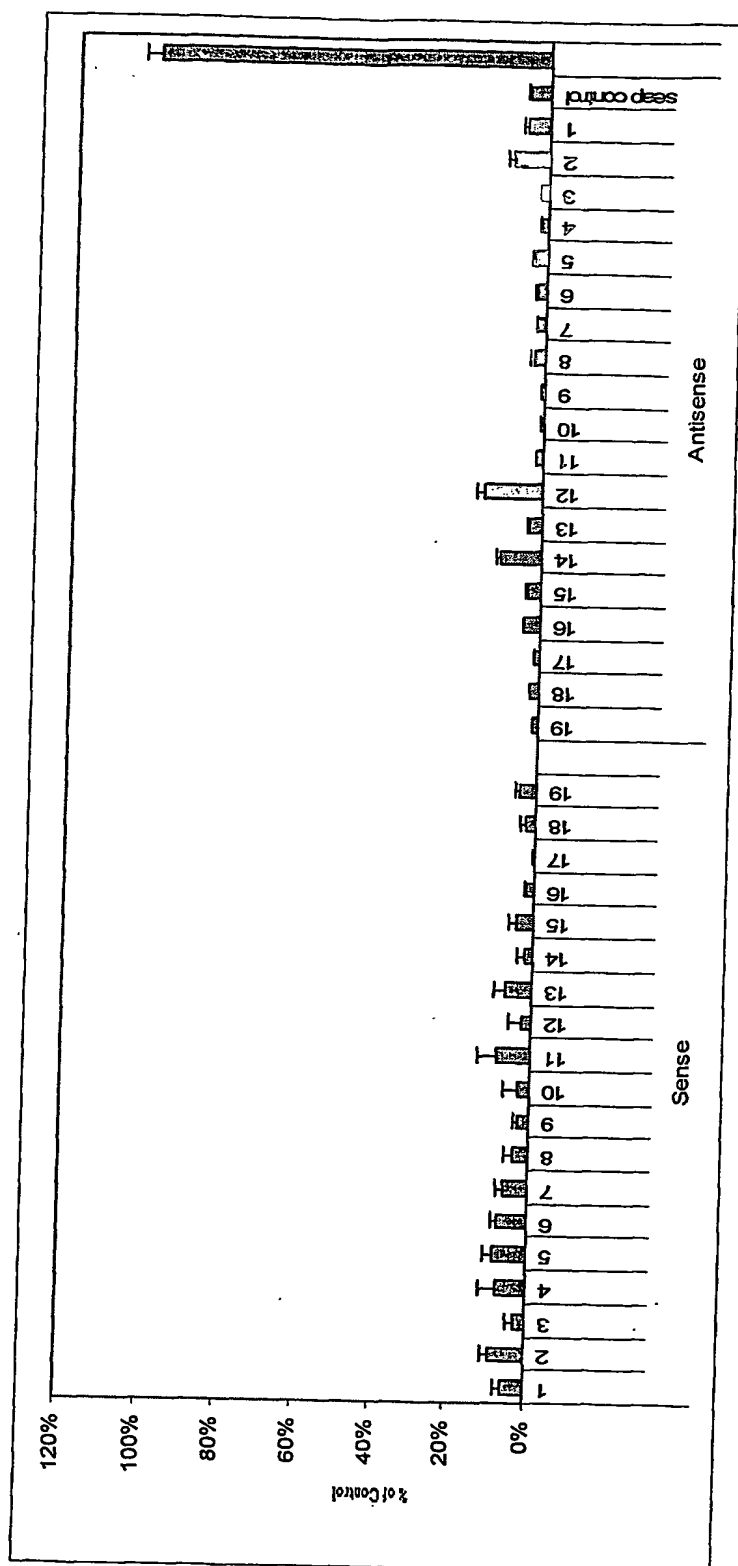


Figure 16A: Single 2'-O-Methyl Modification

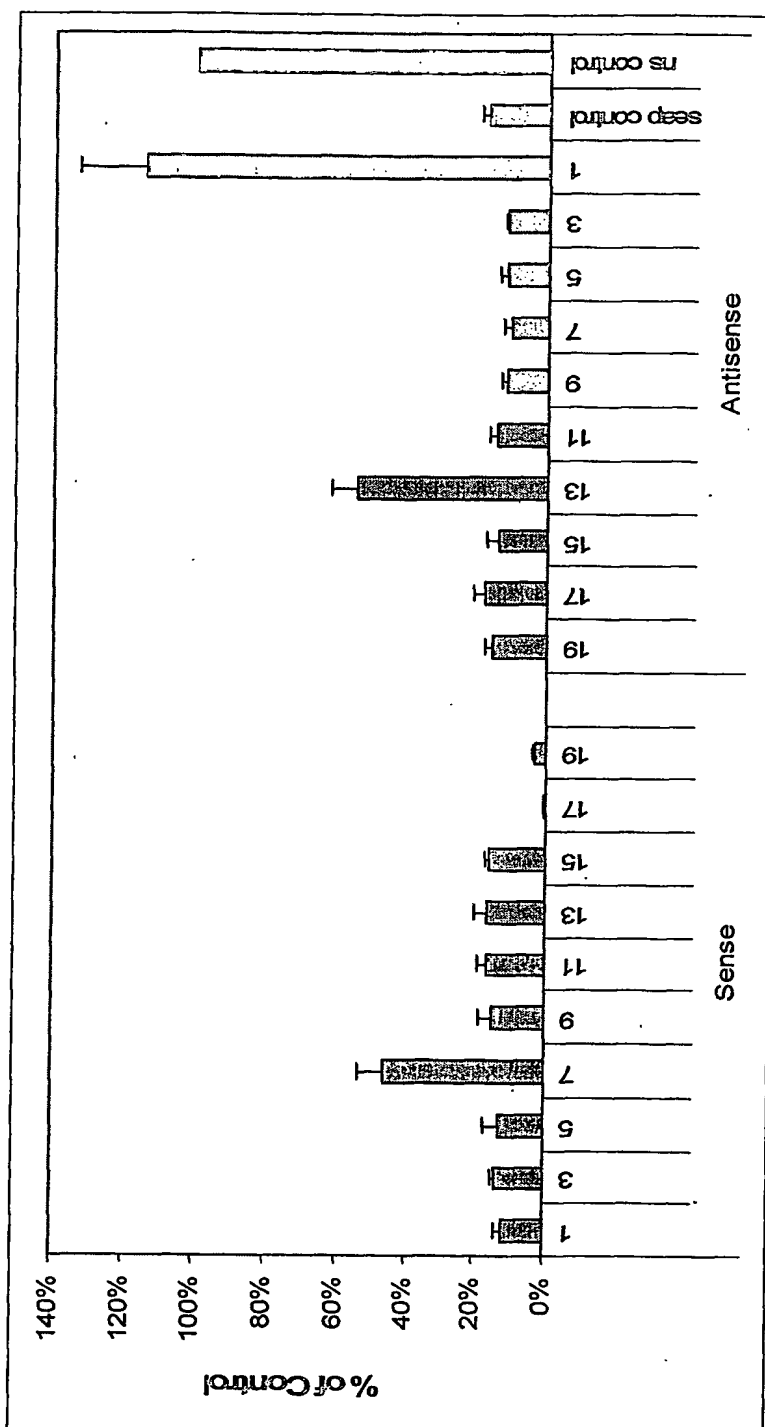


Figure 16B: Two 2'-O-Methyl Modifications in Tandem

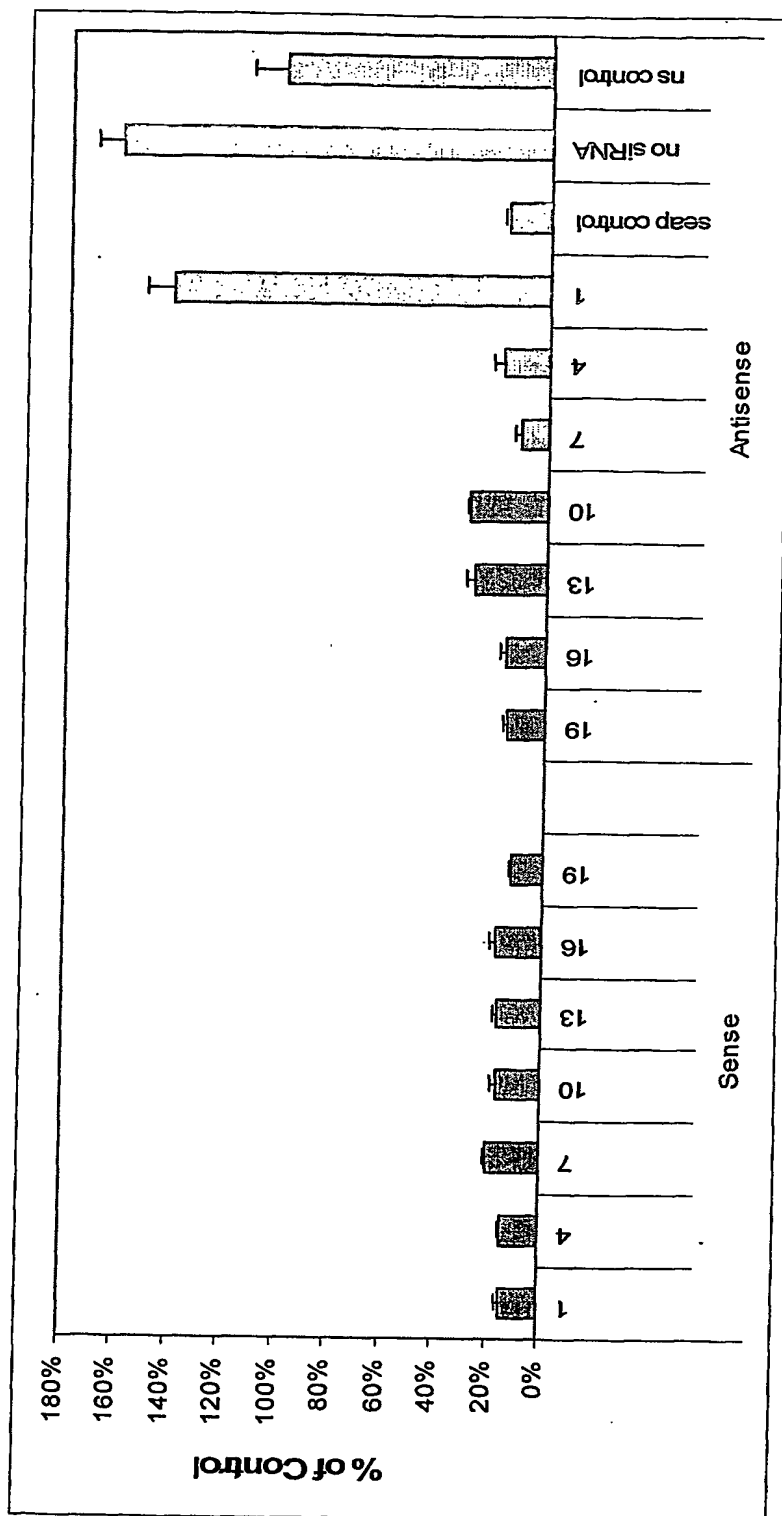


Figure 16C: Three 2'-O-Methyl Modifications in Tandem

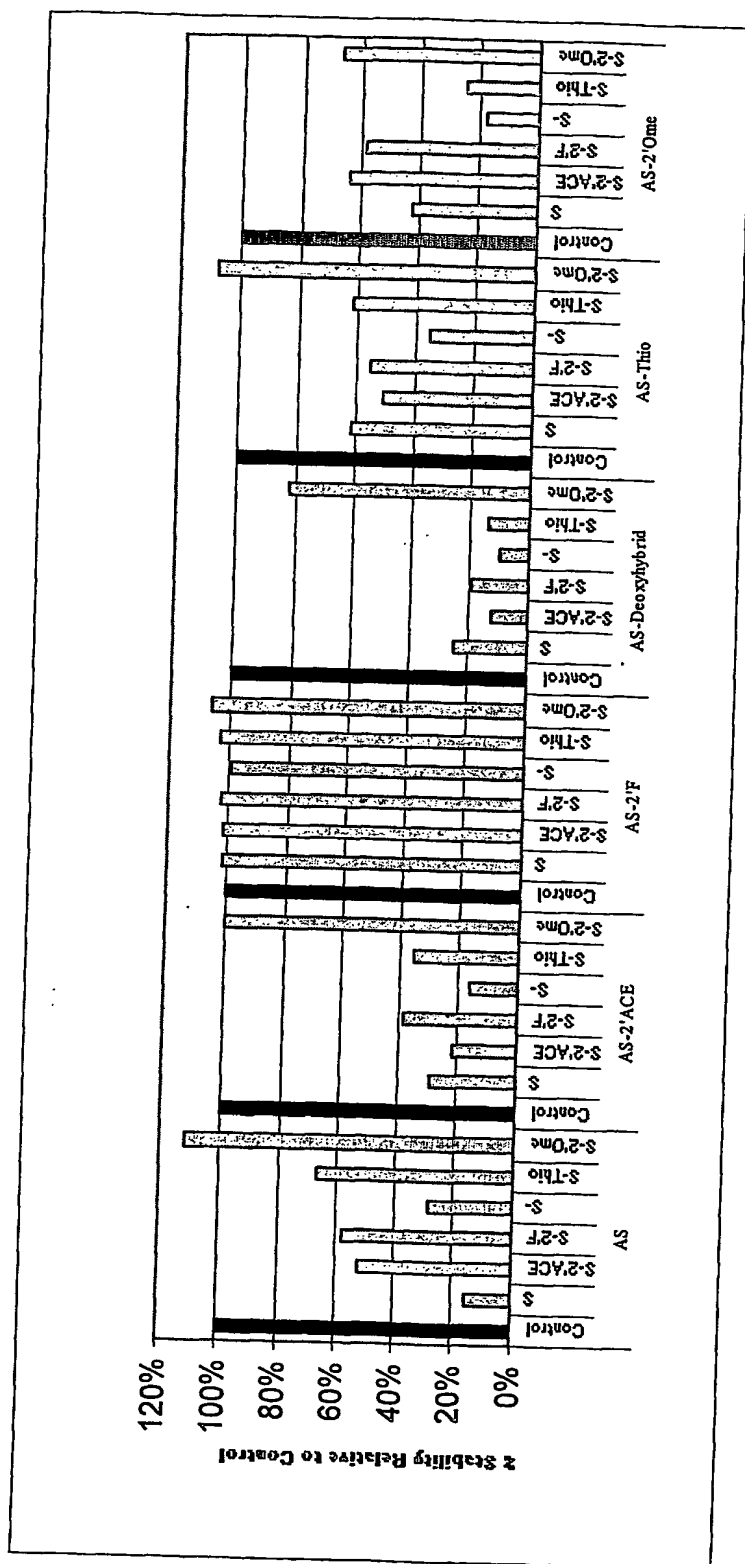


Figure 17: Stability Screen for One Hour Incubation in Media



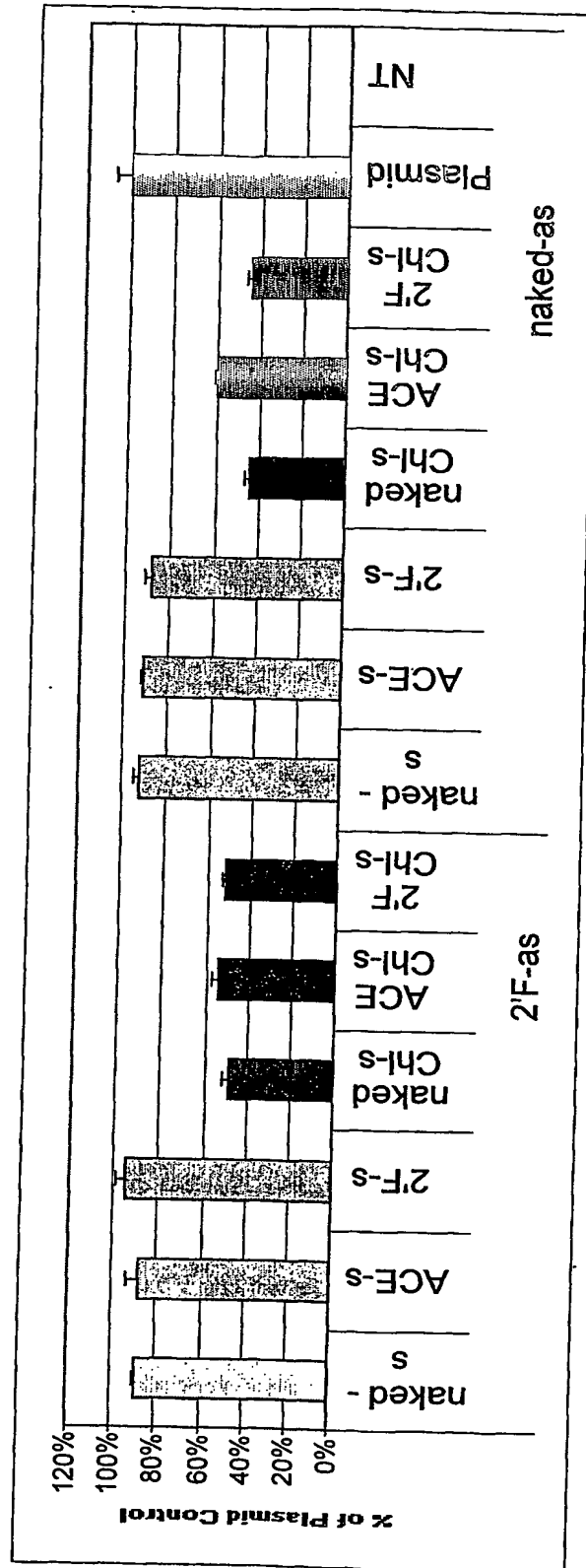


Figure 18: Effect of Cholesterol Modification on Passive Delivery of siRNA

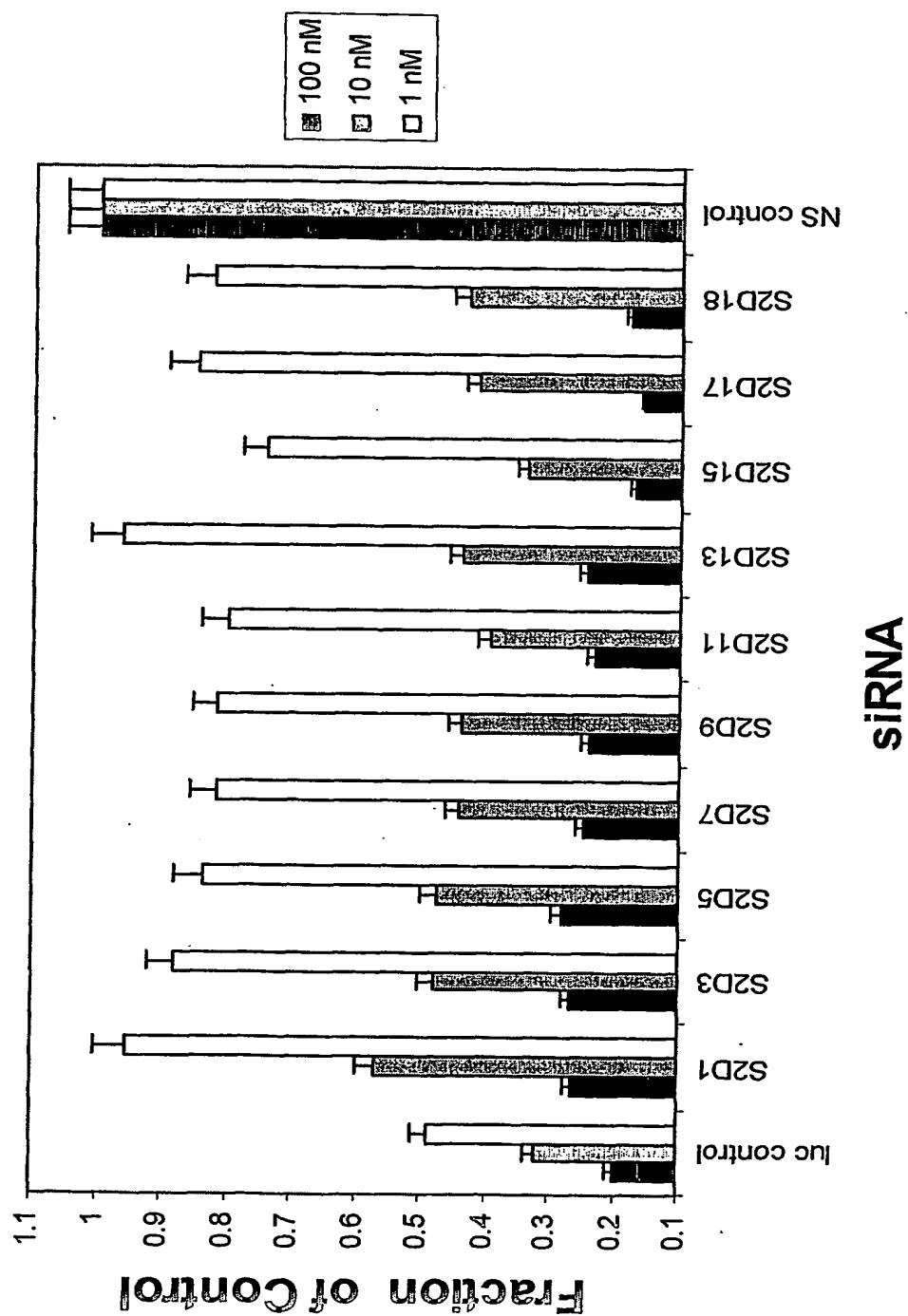


Figure 19: Modification interference screen: blocks of 2 deoxy in the sense strand

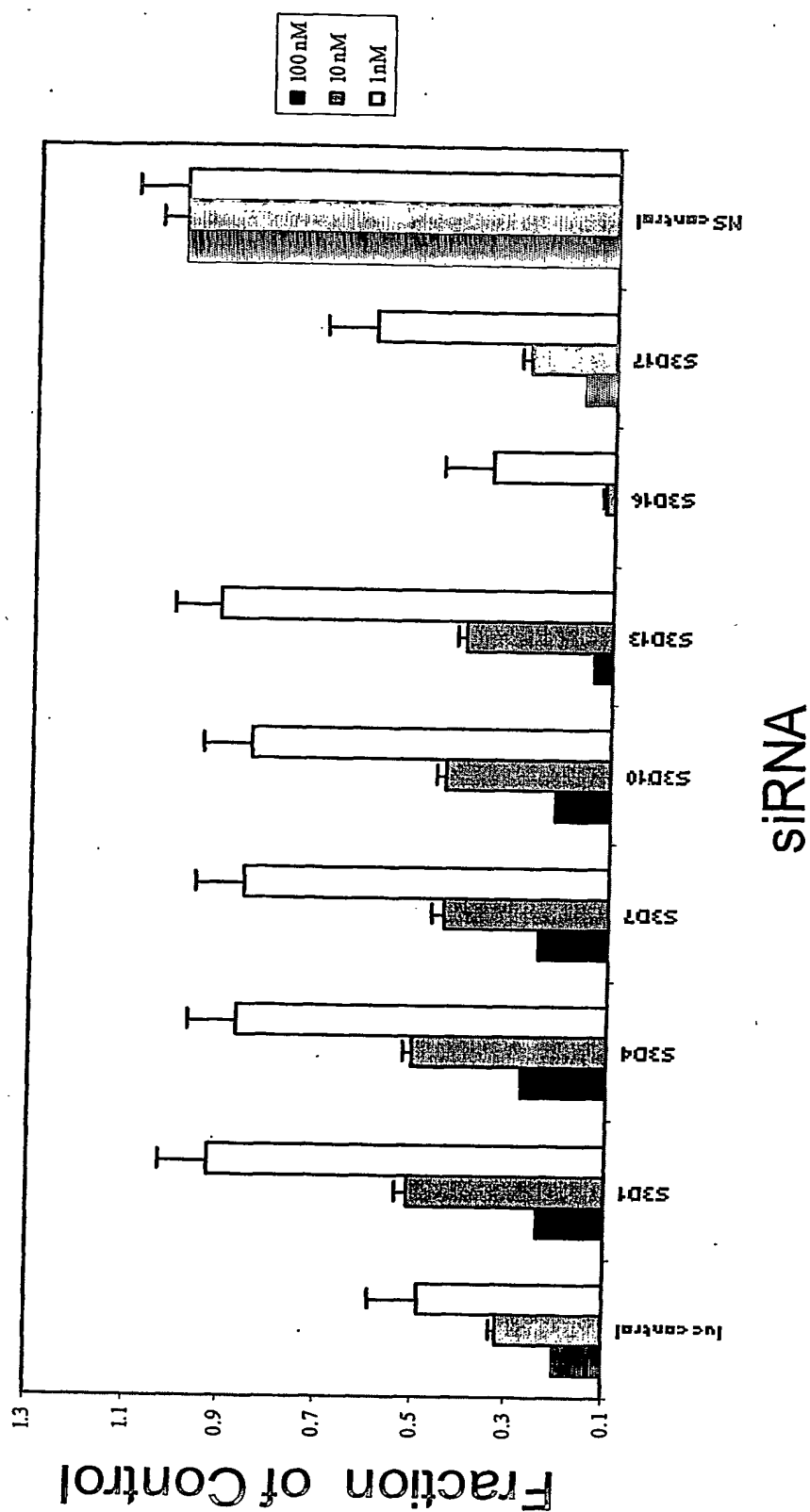


Figure 20: Modification interference screen: blocks of 3 deoxy in the sense strand

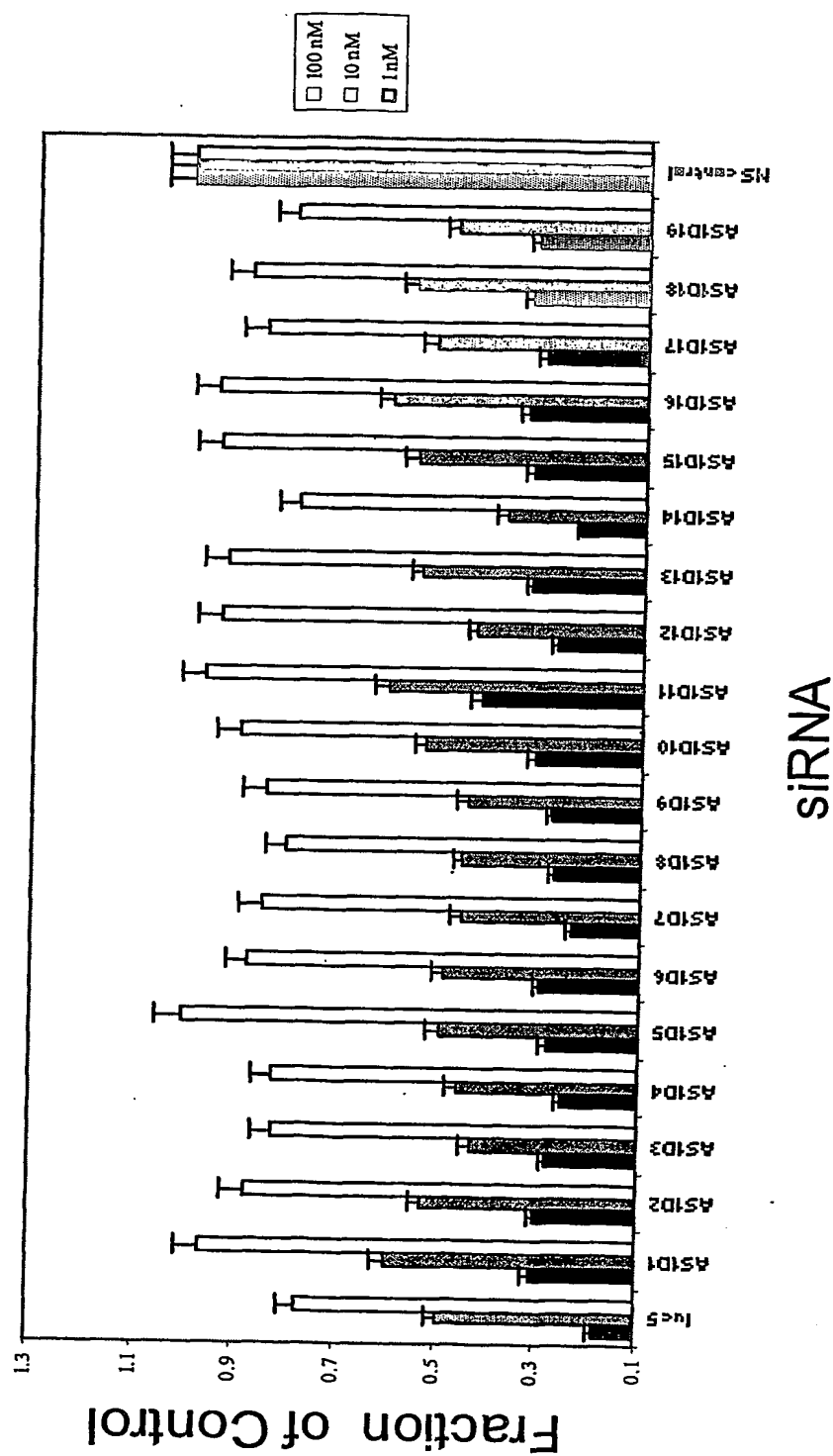


Figure 21: Modification interference screen: deoxy in the antisense strand

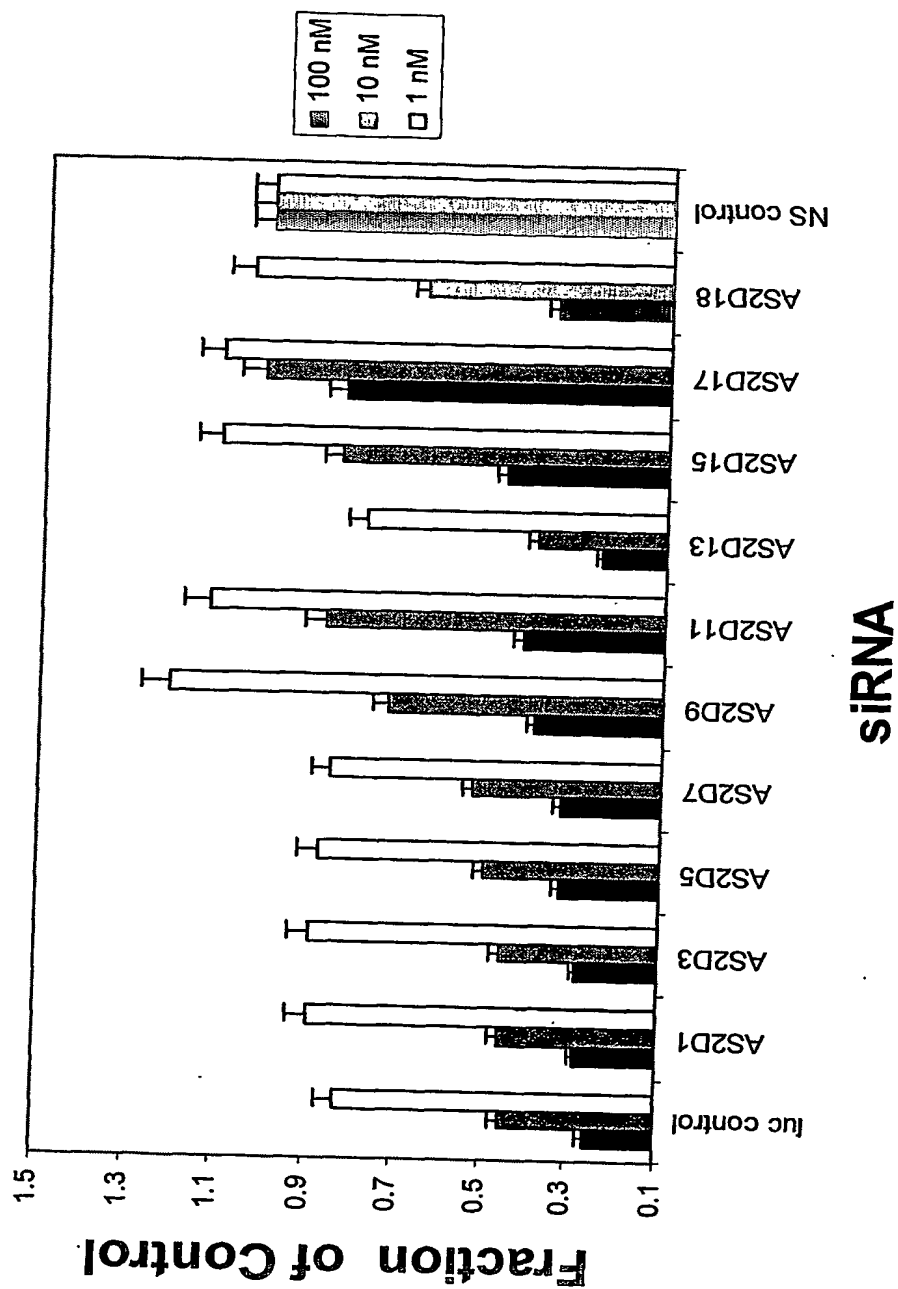


Figure 22: Modification interference screen: blocks of 2 deoxy in the antisense strand

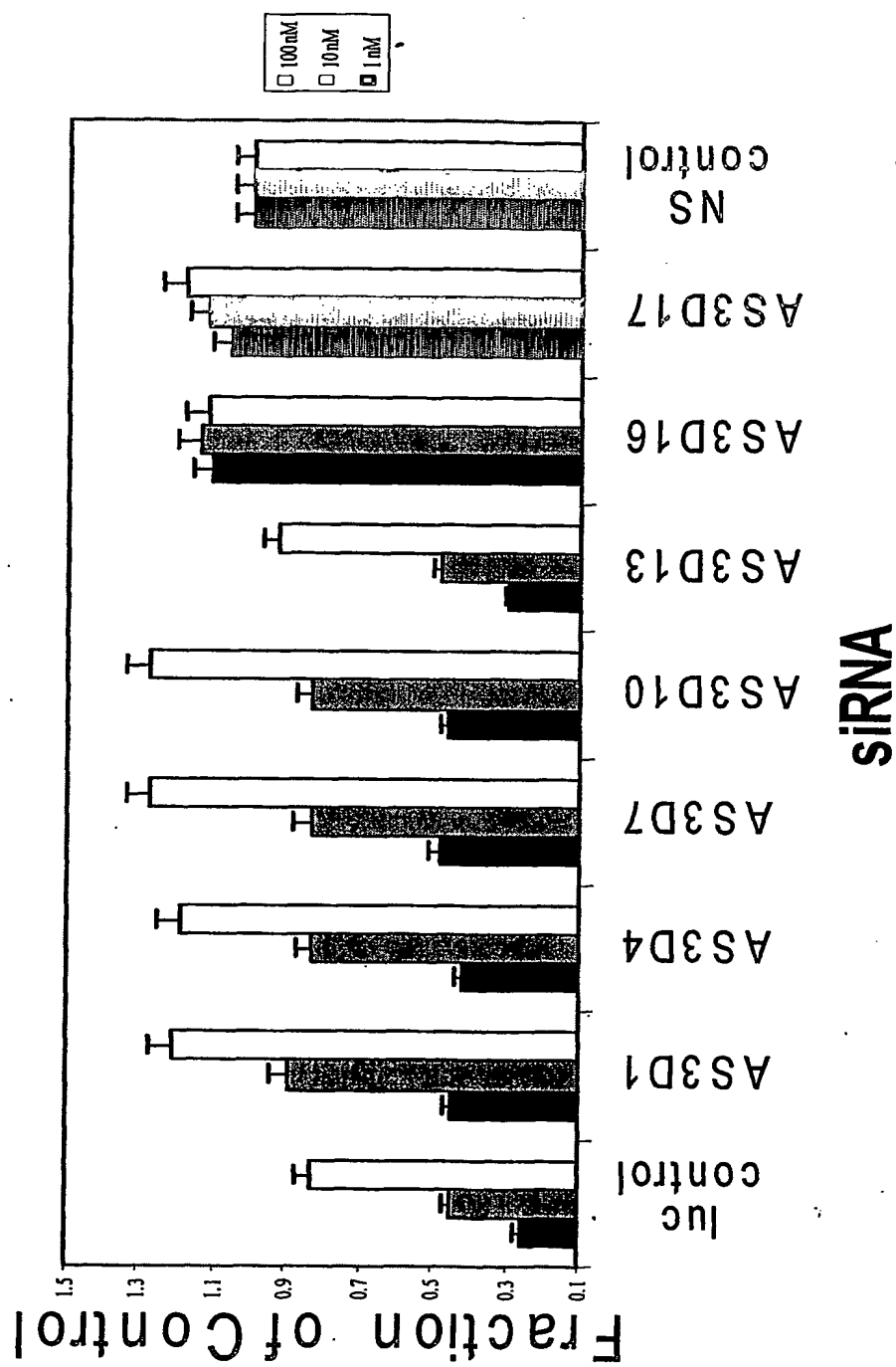


Figure 23: Modification interference screen: blocks of 3 deoxy in the antisense strand

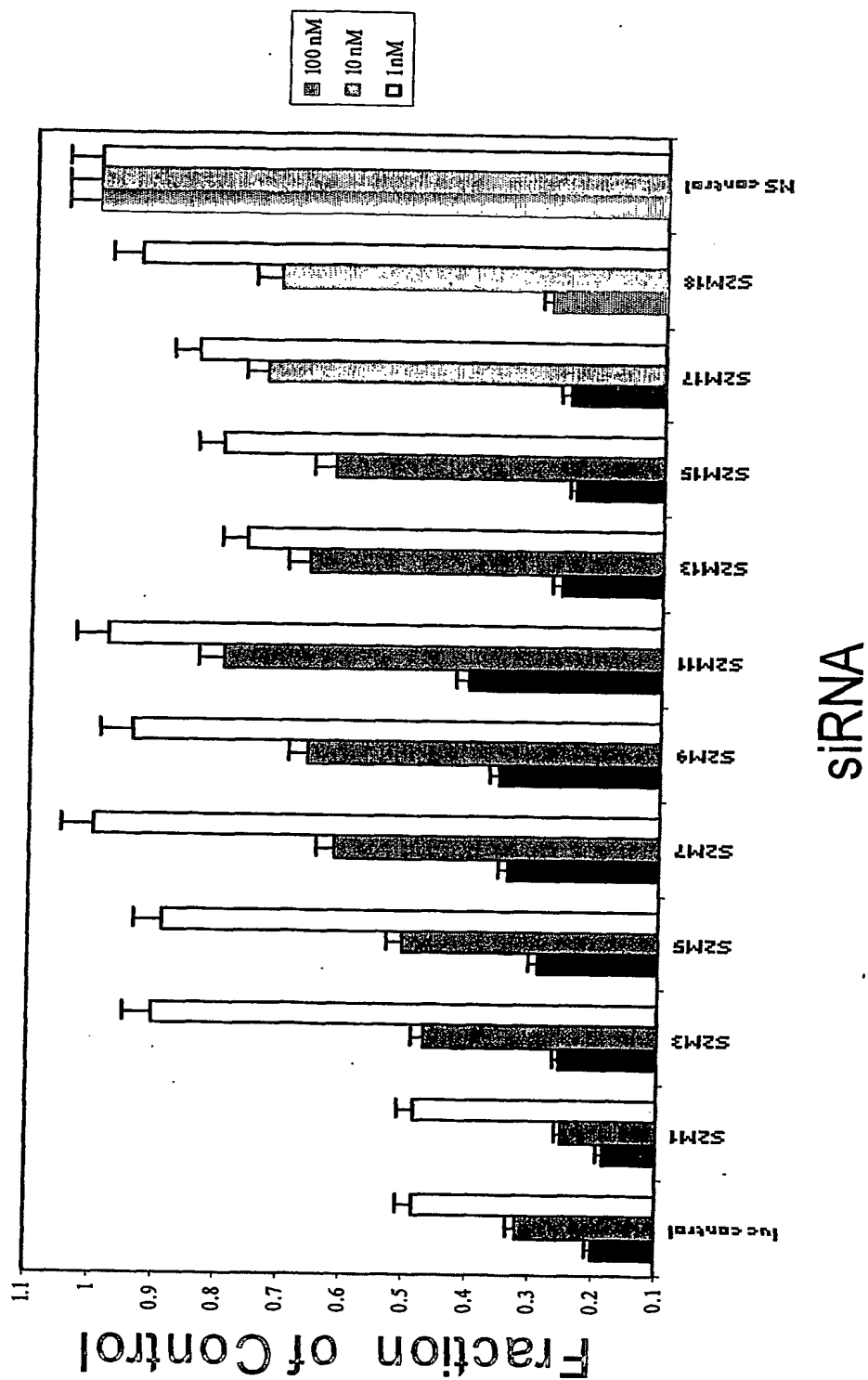
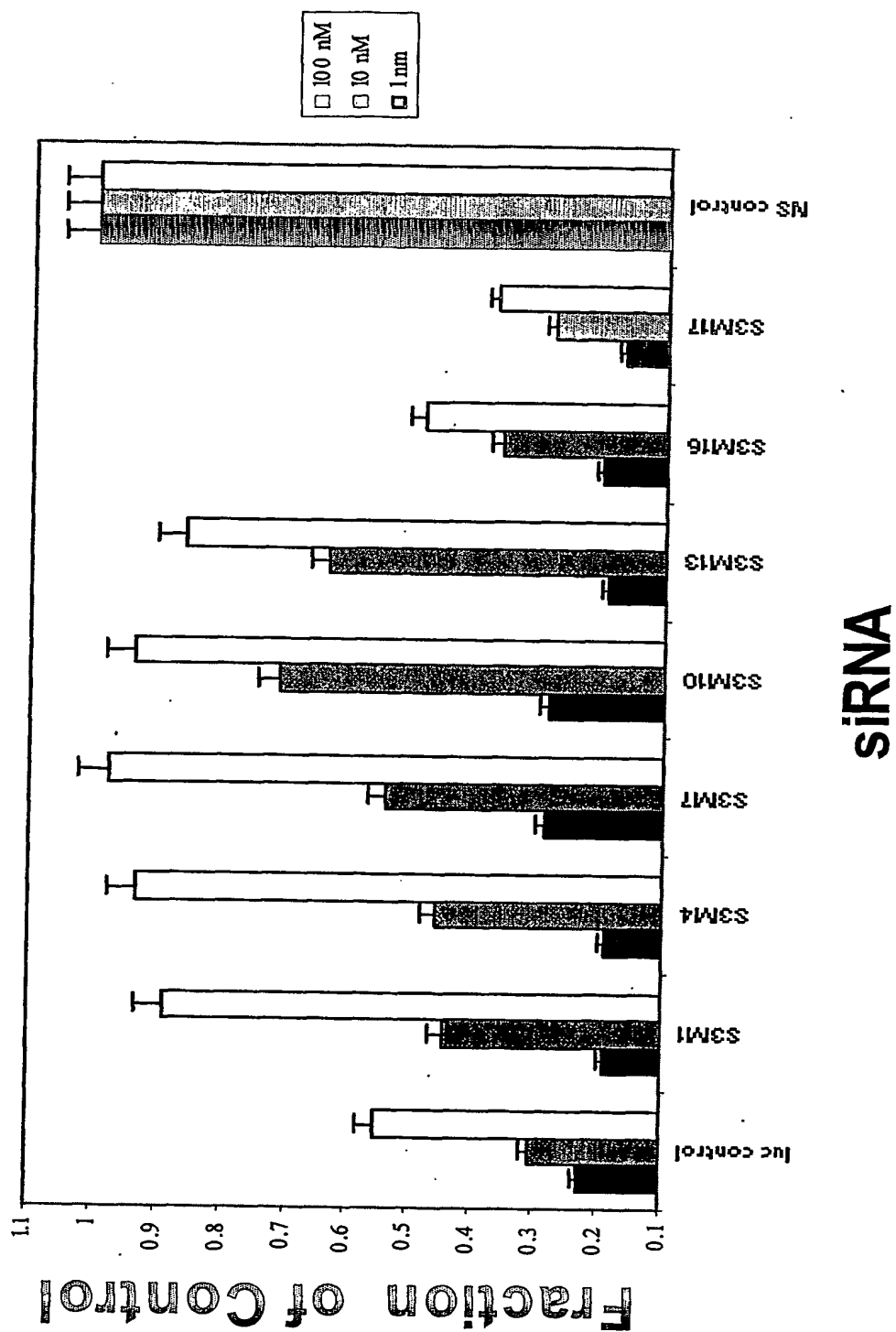


Figure 24: Modification interference screen: blocks of 2 methoxy in the sense strand



**Figure 25: Modification interference screen: blocks of 3 methoxy in the sense strand**



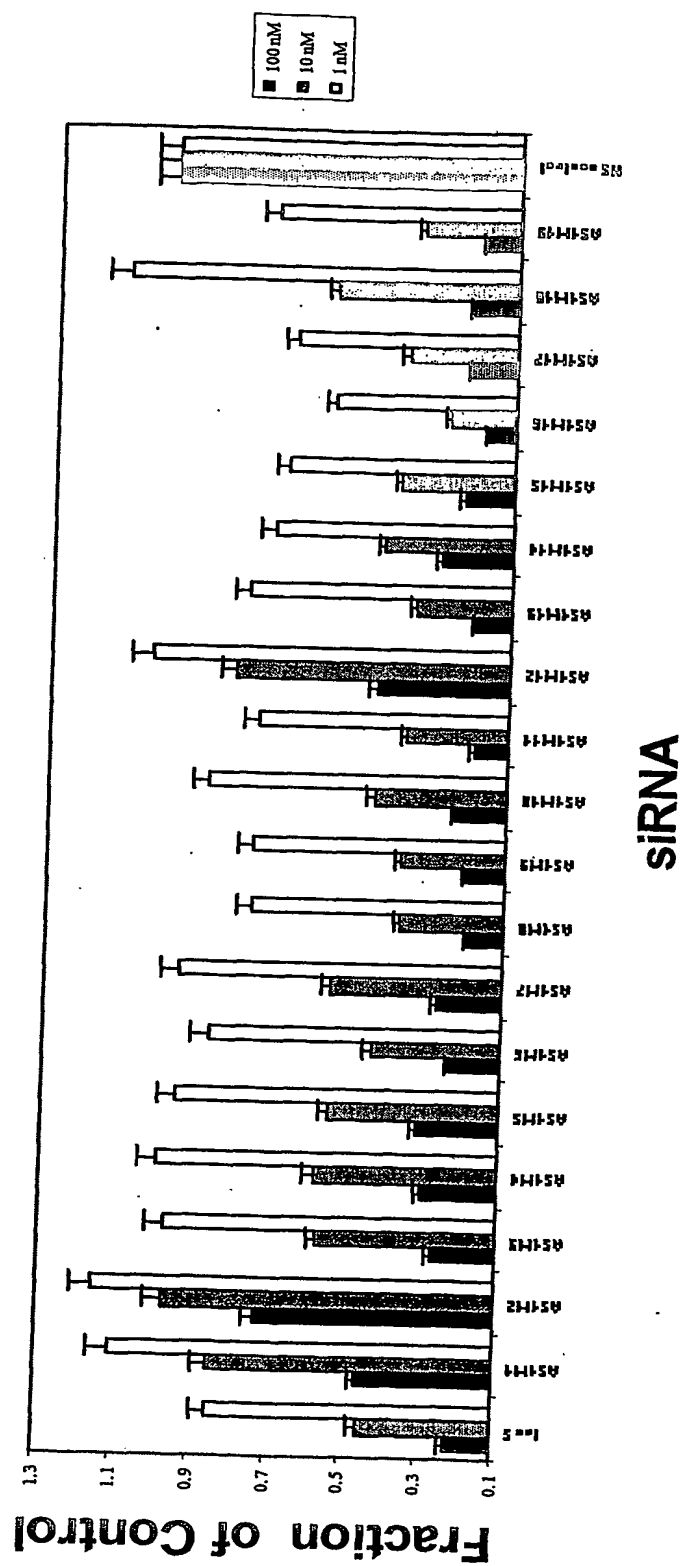


Figure 26: Modification interference screen: 2'-O-methyl in the antisense strand

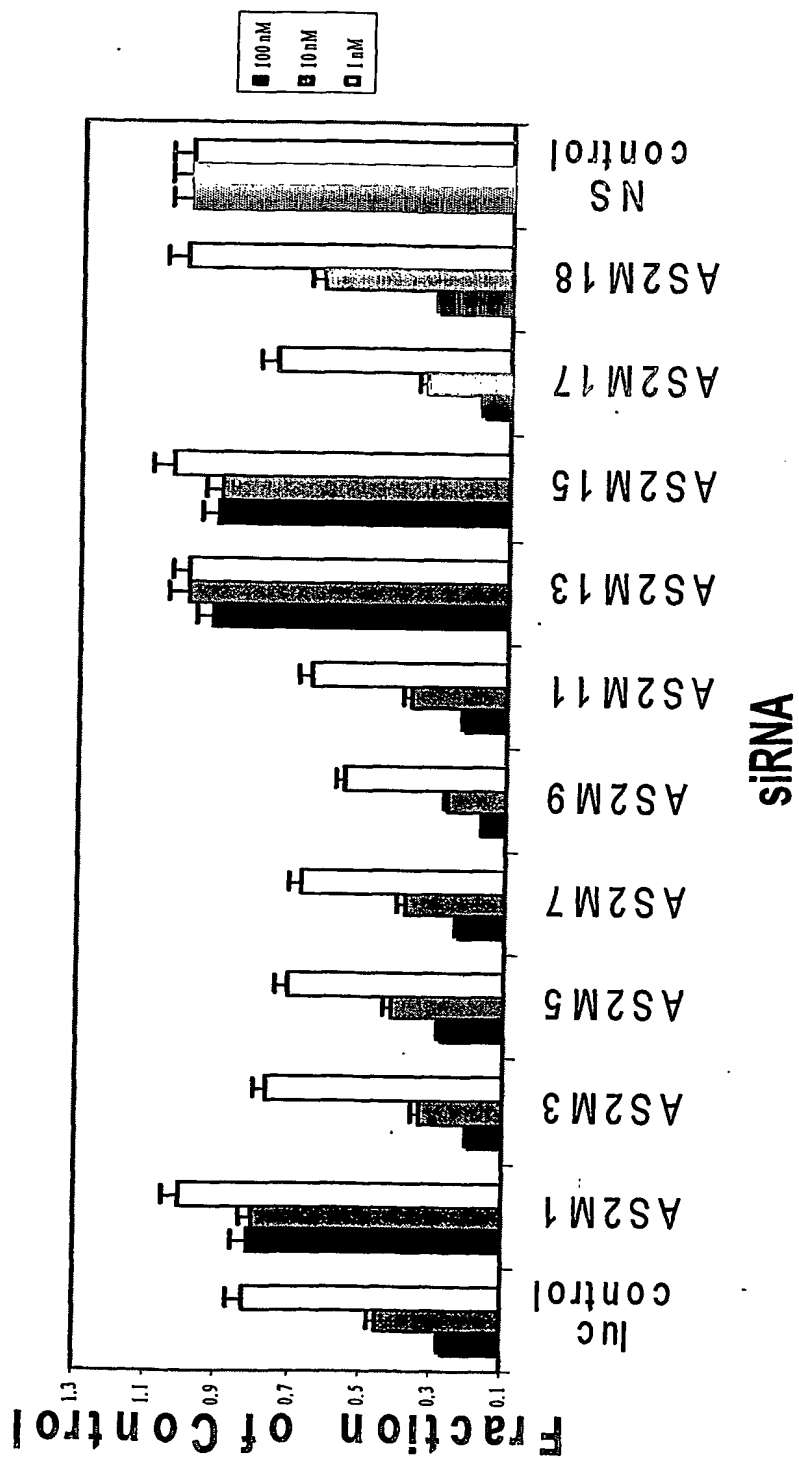


Figure 27: Modification interference screen: blocks of two 2'-O-methyl in the antisense strand

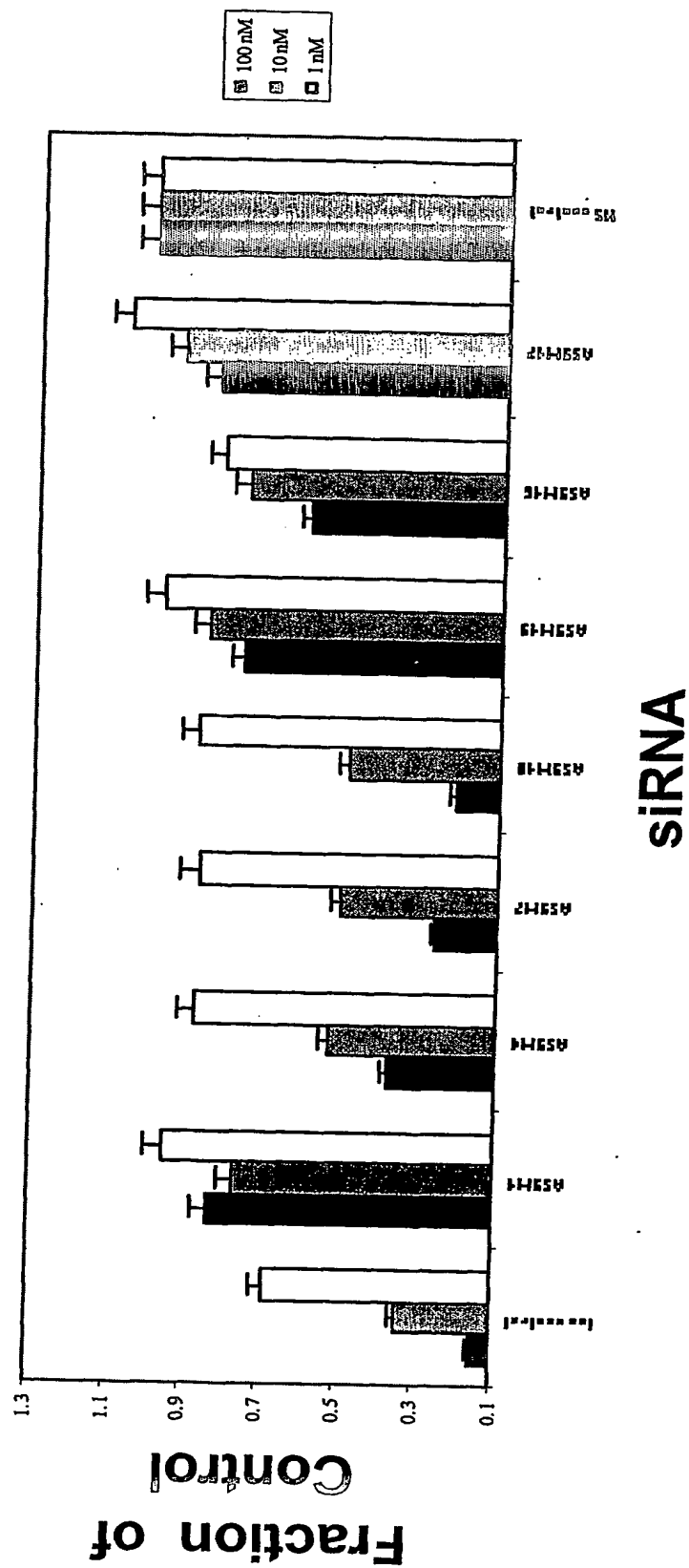


Figure 28: Modification interference screen: blocks of three 2'-O-methyl in the antisense strand

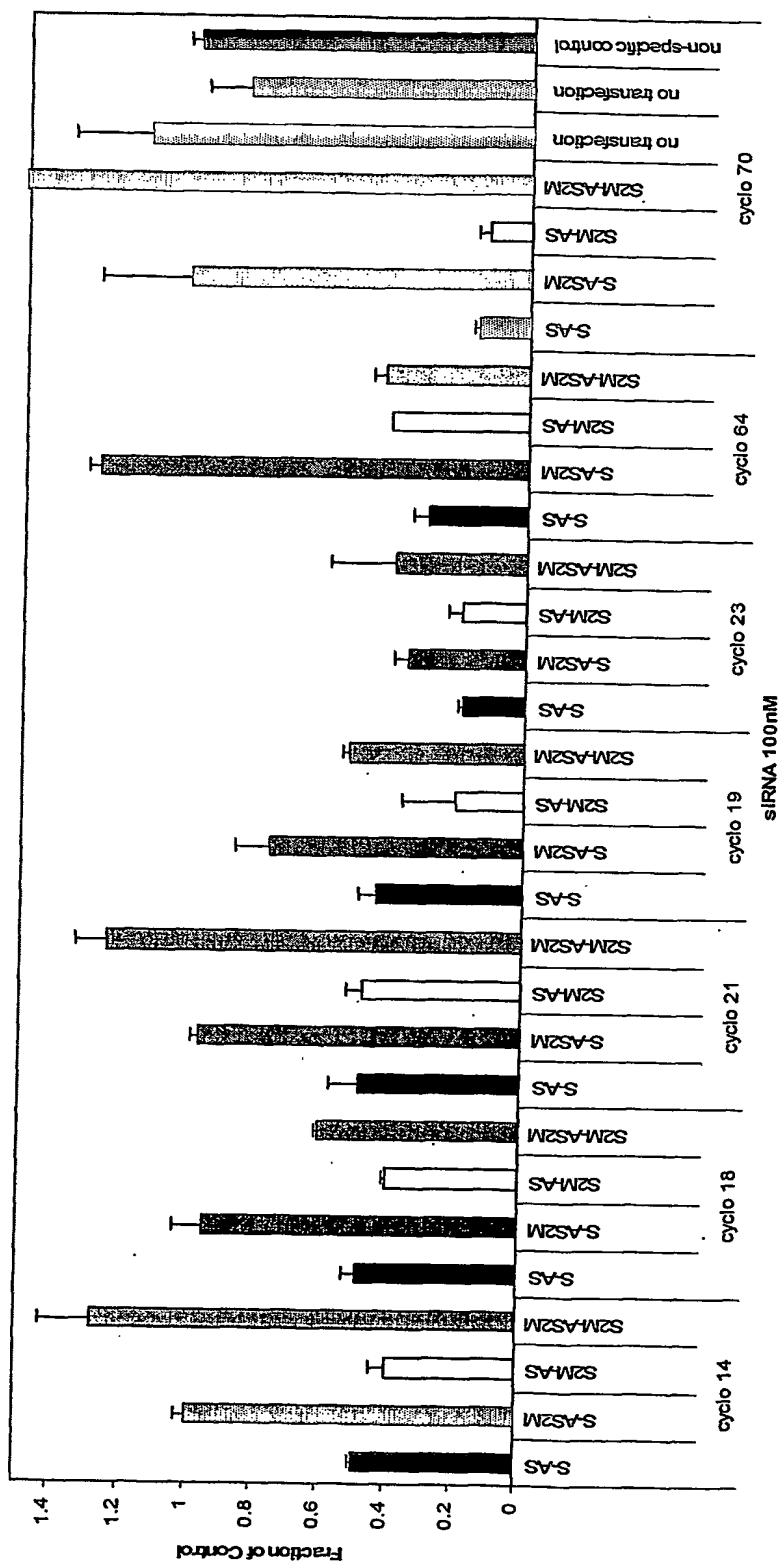
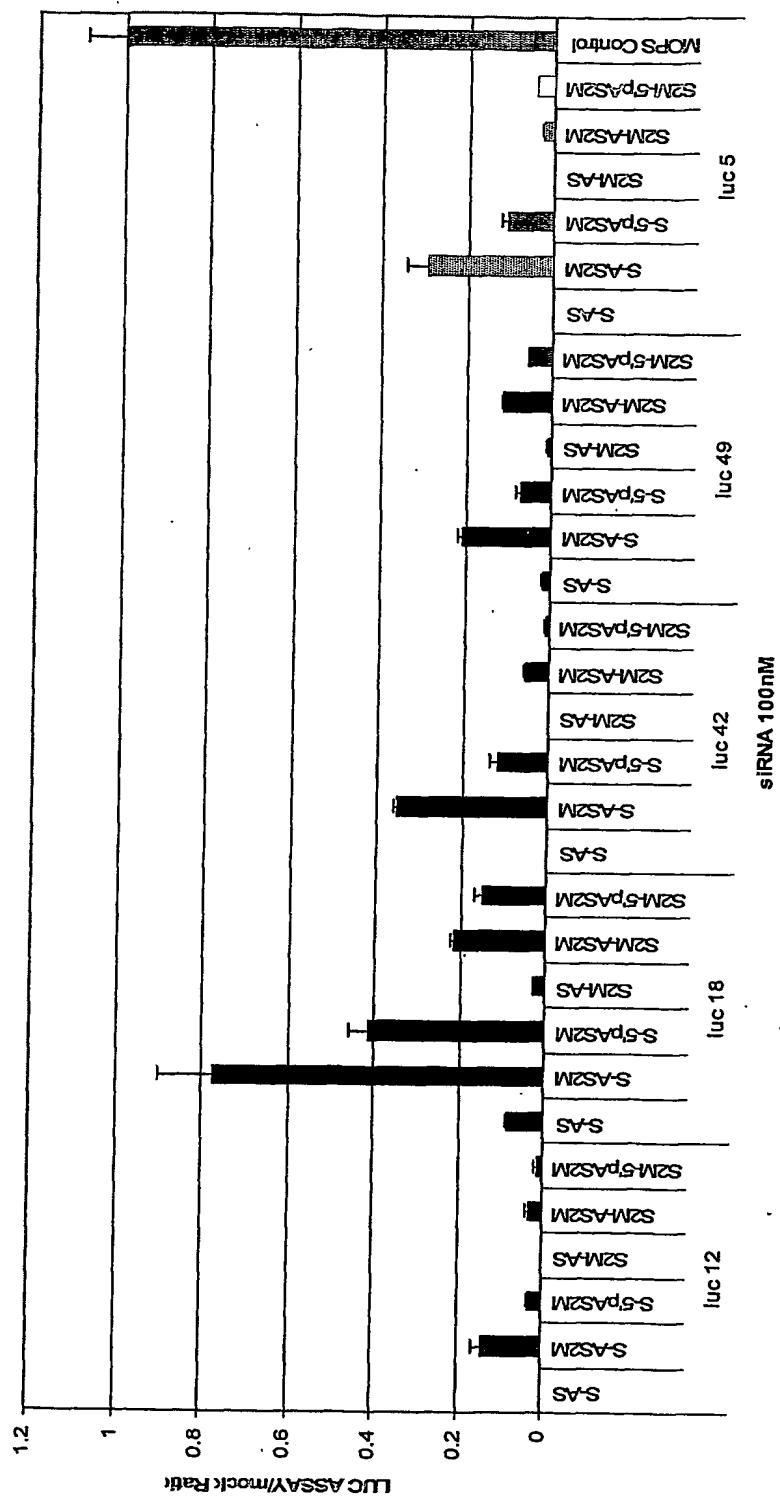


Figure 29: Presence of the 2'-2'Ome modifications result on the 5'AS strand interfere with functionality in human Cyclophilin



**Figure 30: Presence of the 2'-2'Ome modifications result on the 5' AS strand interfere with functionality in the Firefly Luciferase in 293 Cells**

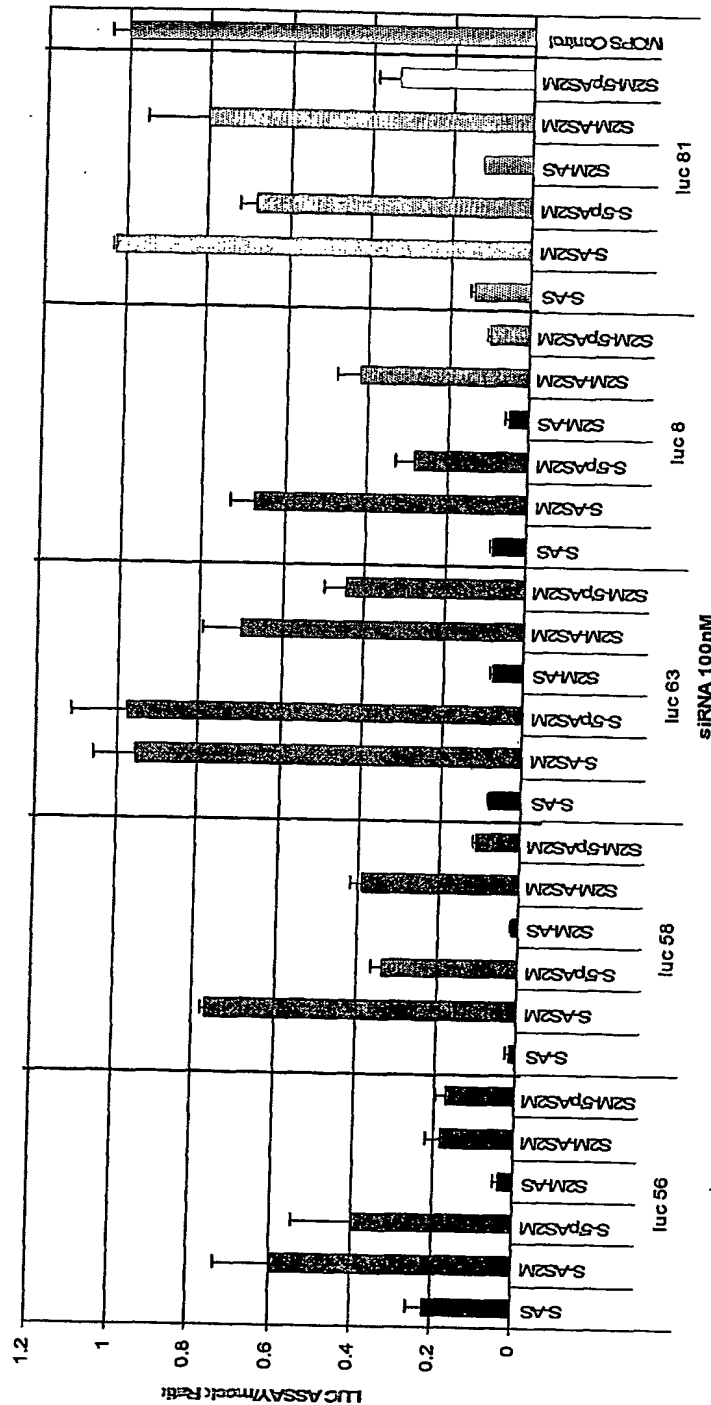


Figure 31: Presence of the 2'-2'Ome modifications result on the 5'AS strand interfere with functionality in 293 cells

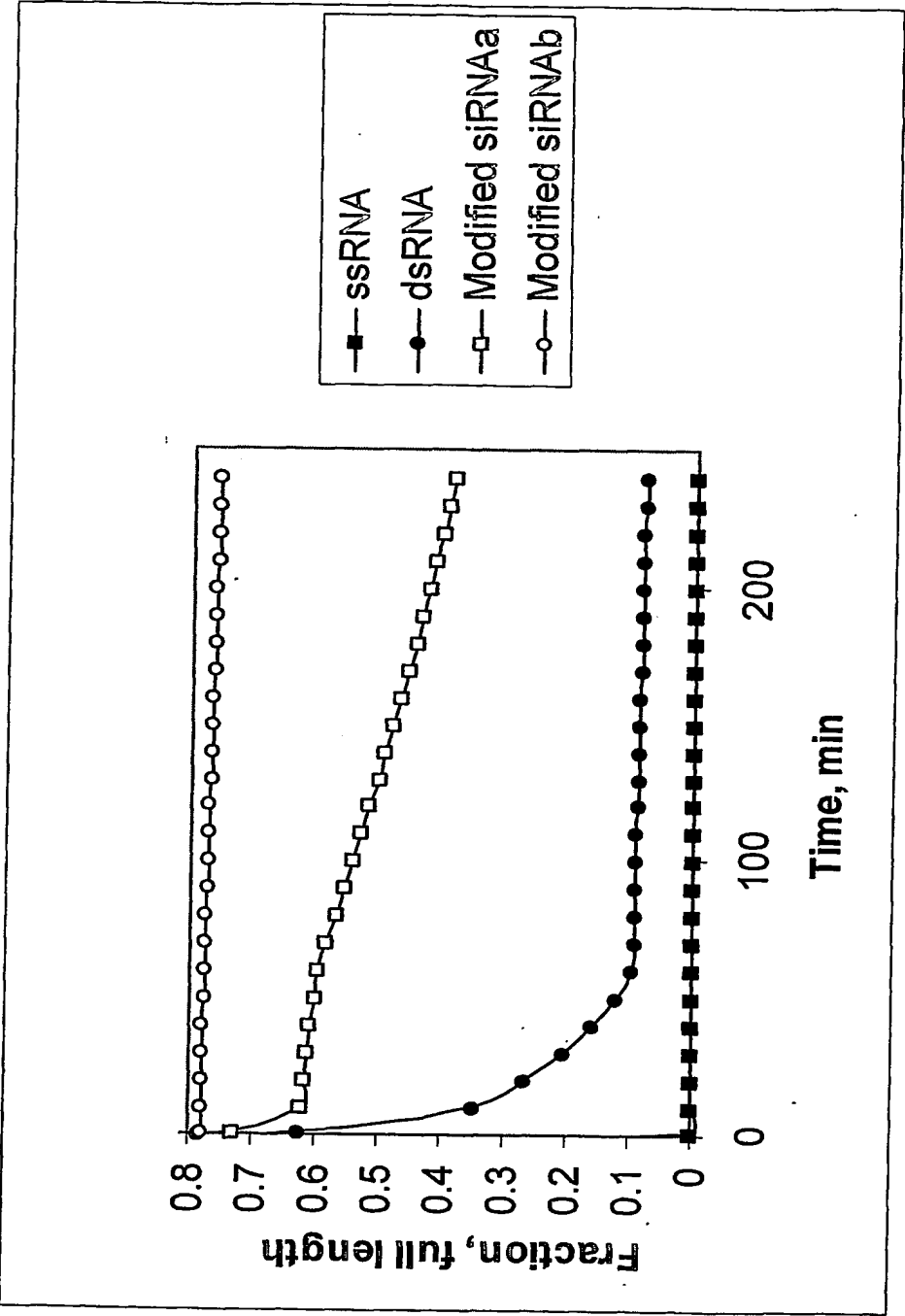


Figure 32: siRNA stability in 100% human serum

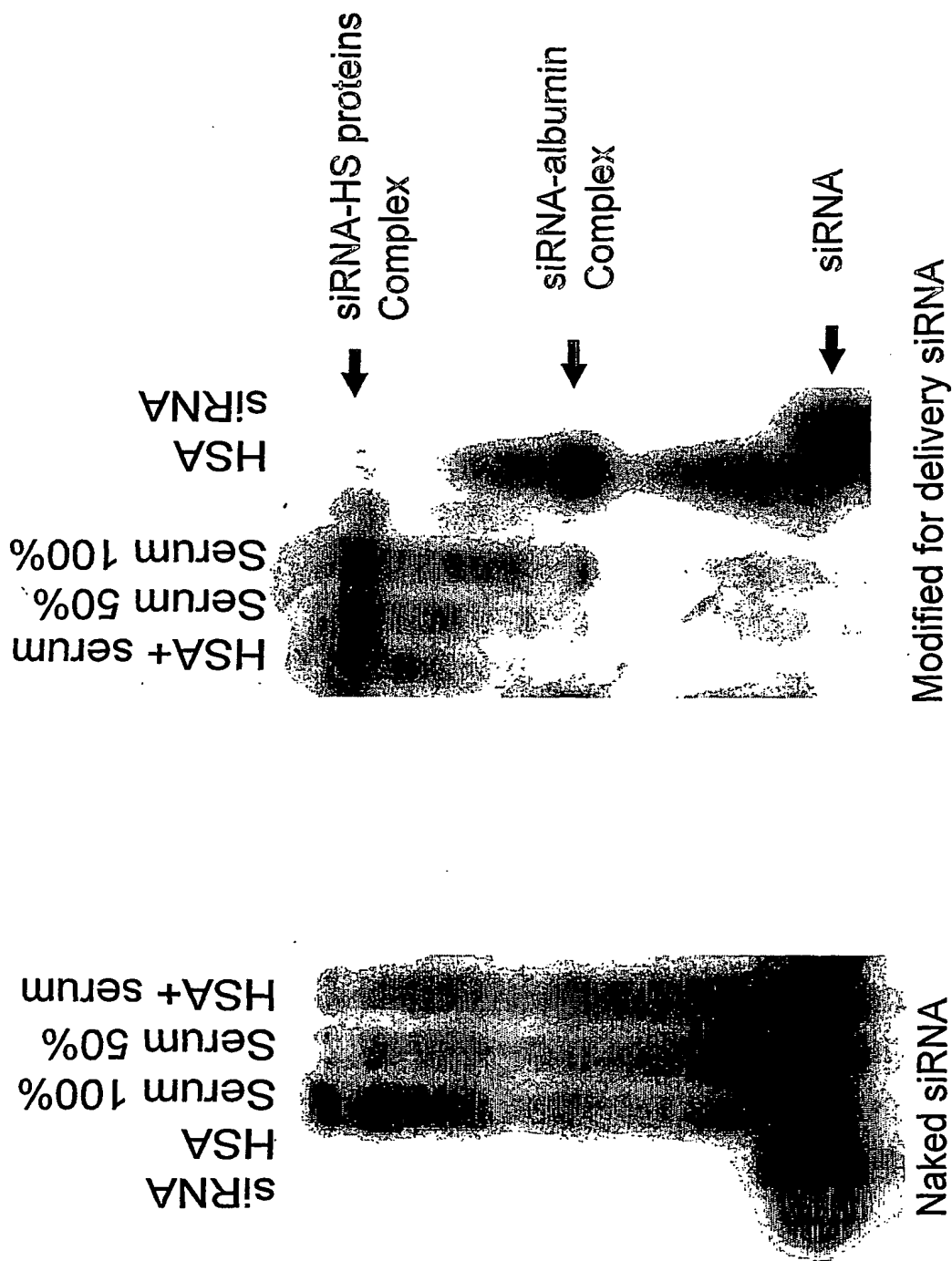


Figure 33: siRNA- cholesterol conjugates has increased affinity to albumin and other serum proteins



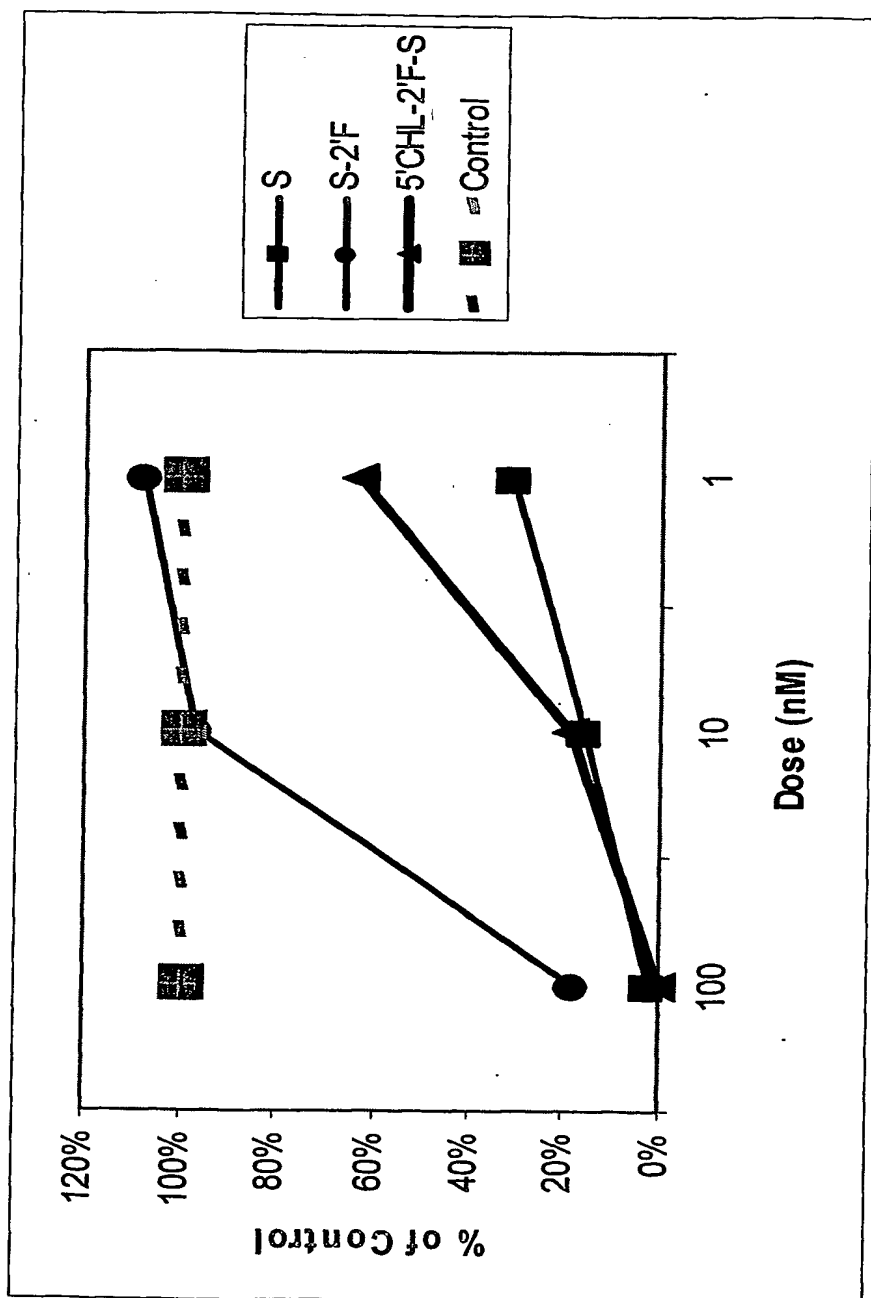


Figure 34: Small Molecule Conjugates Maintain and Accentuate the Potency of Modified siRNA

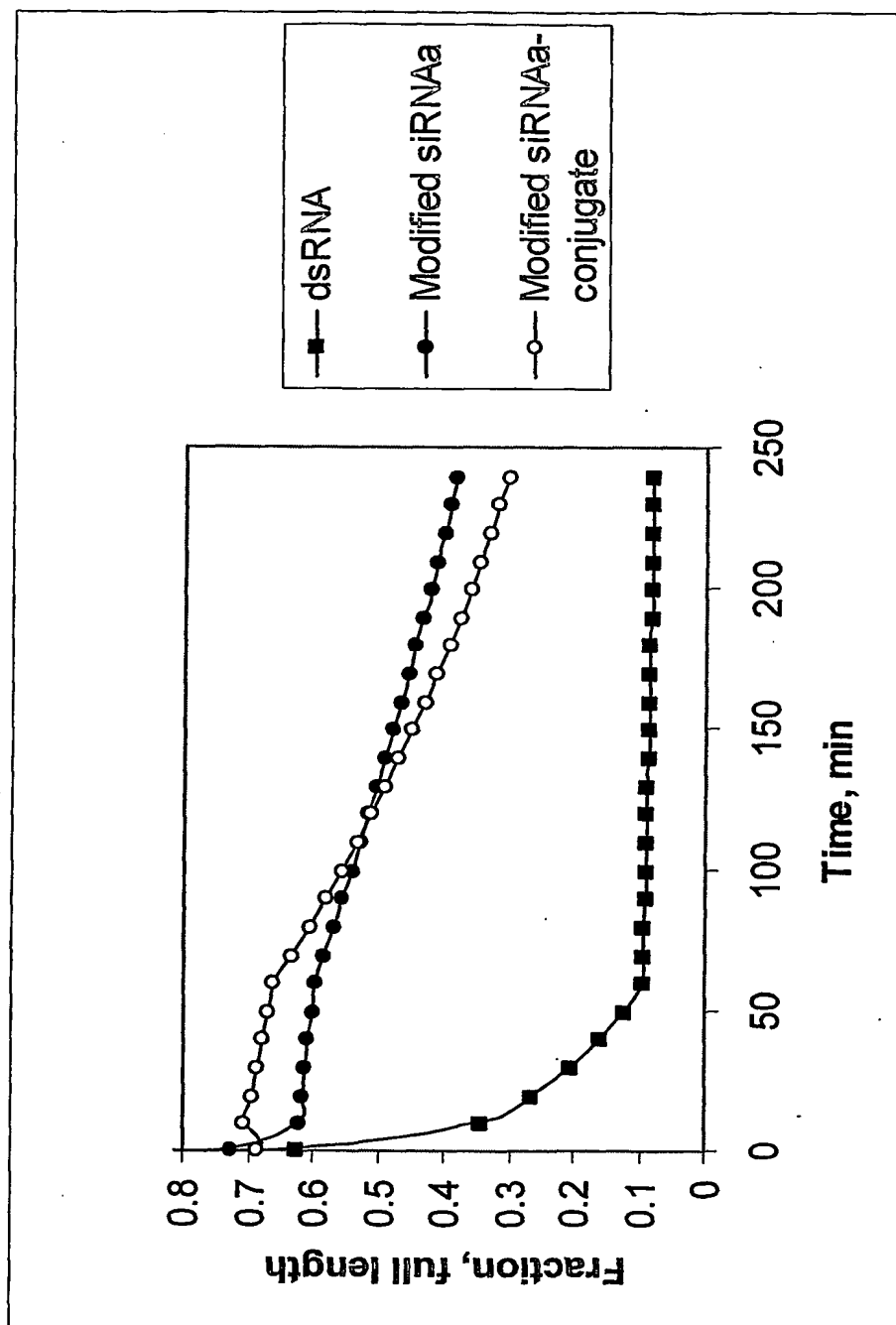
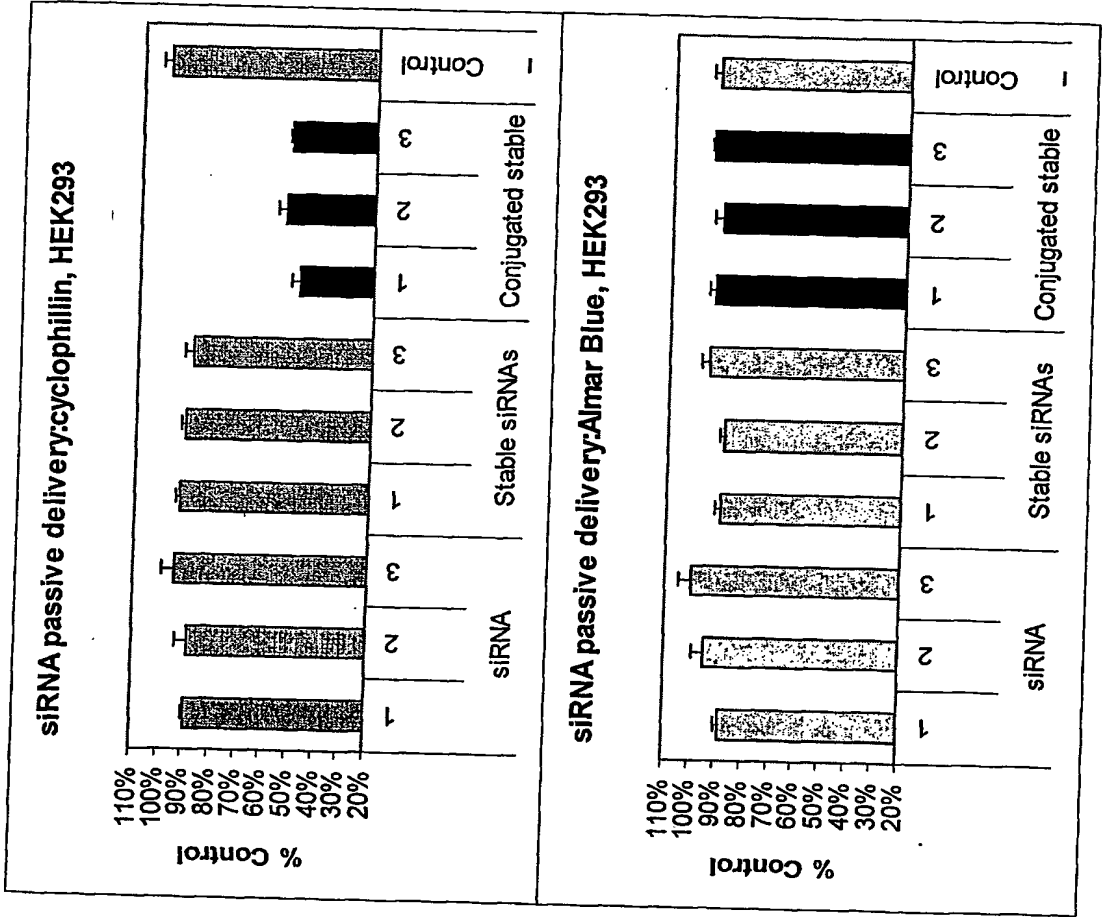


Figure 35: Stability of siRNA conjugates in Human serum



**Figure 36: The cholesterol conjugates may induce the siRNA uptake**

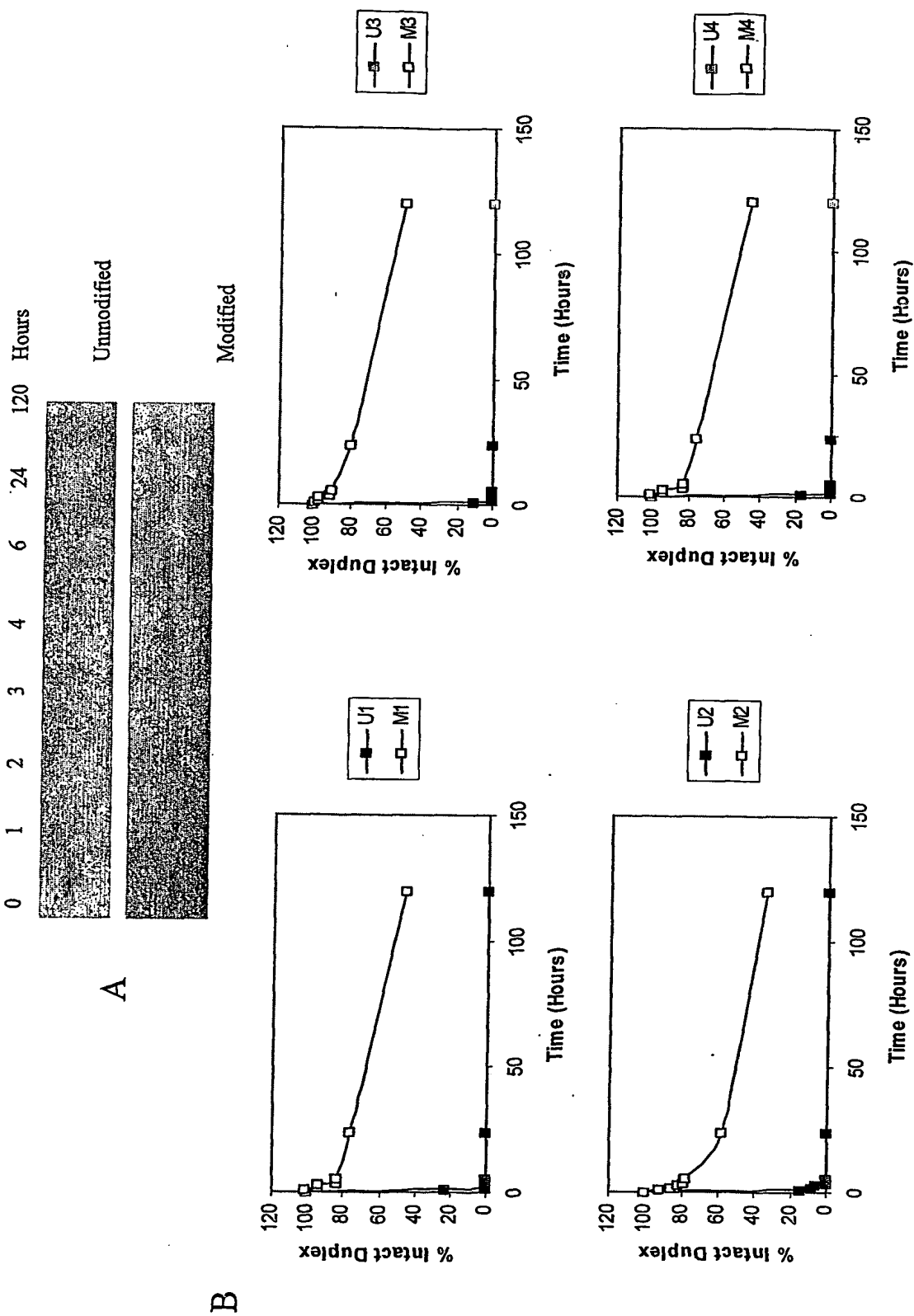


Figure 37

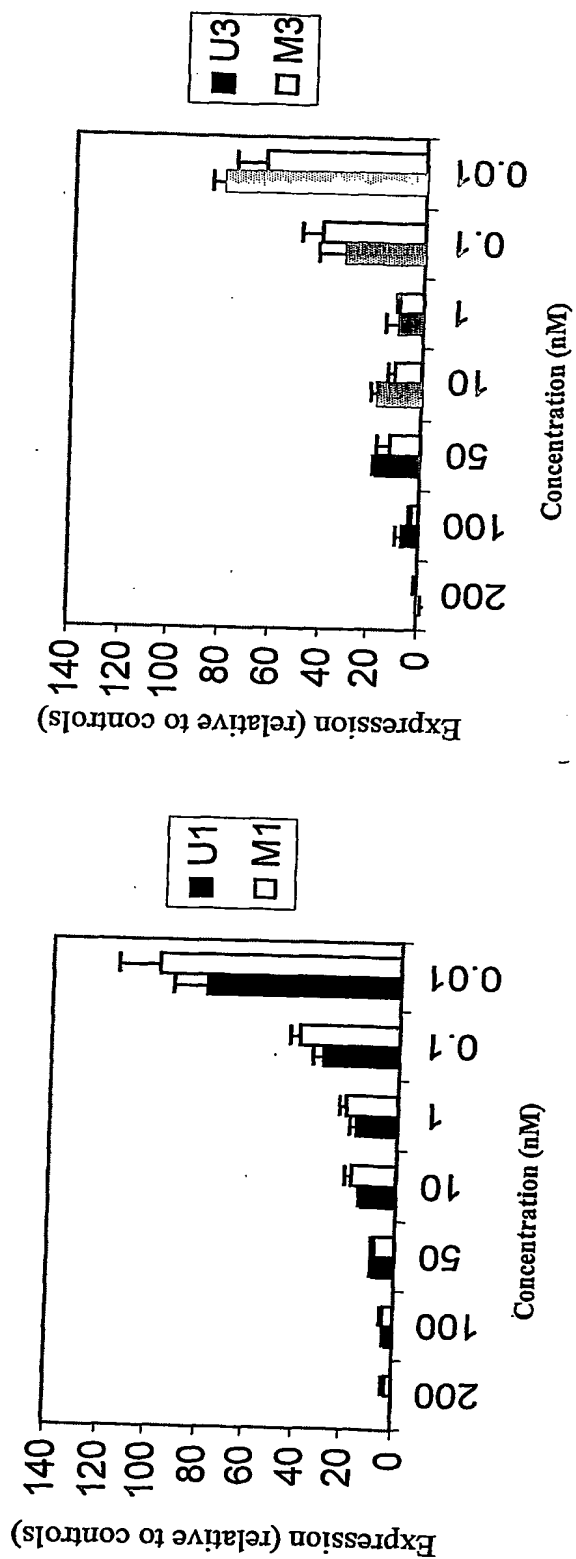


Figure 38

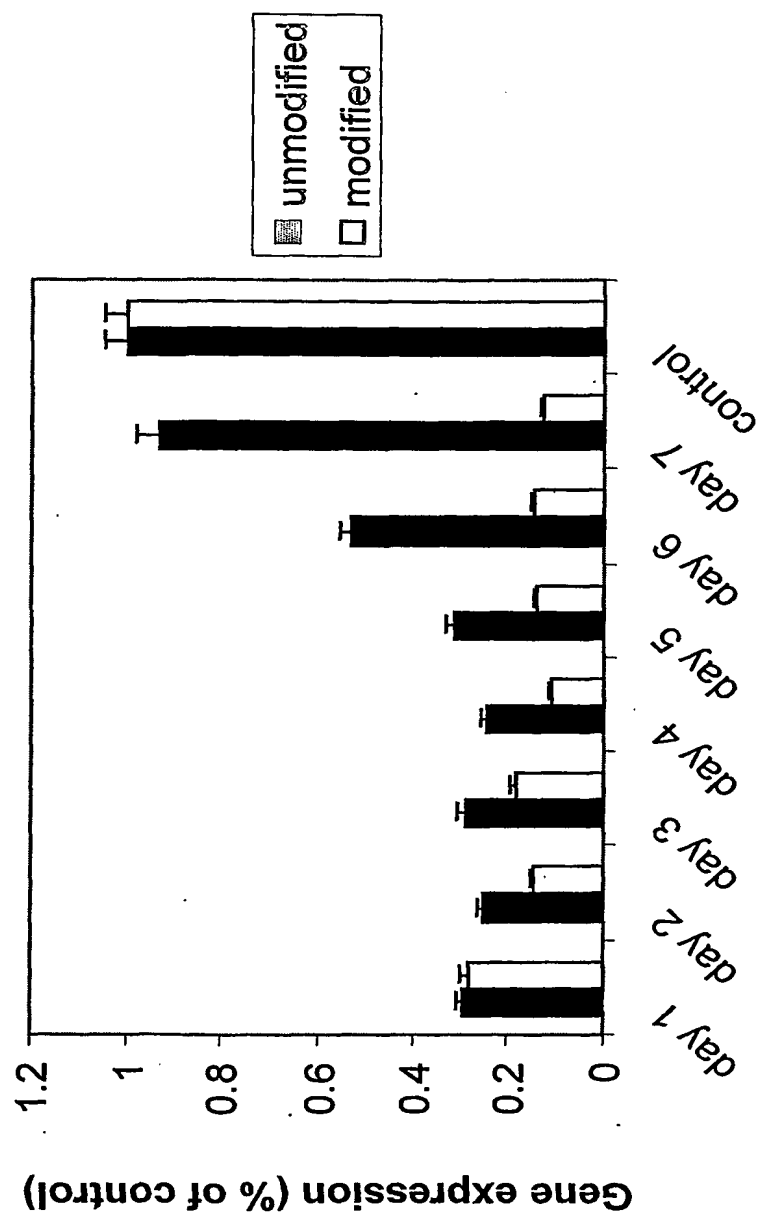


Figure 39

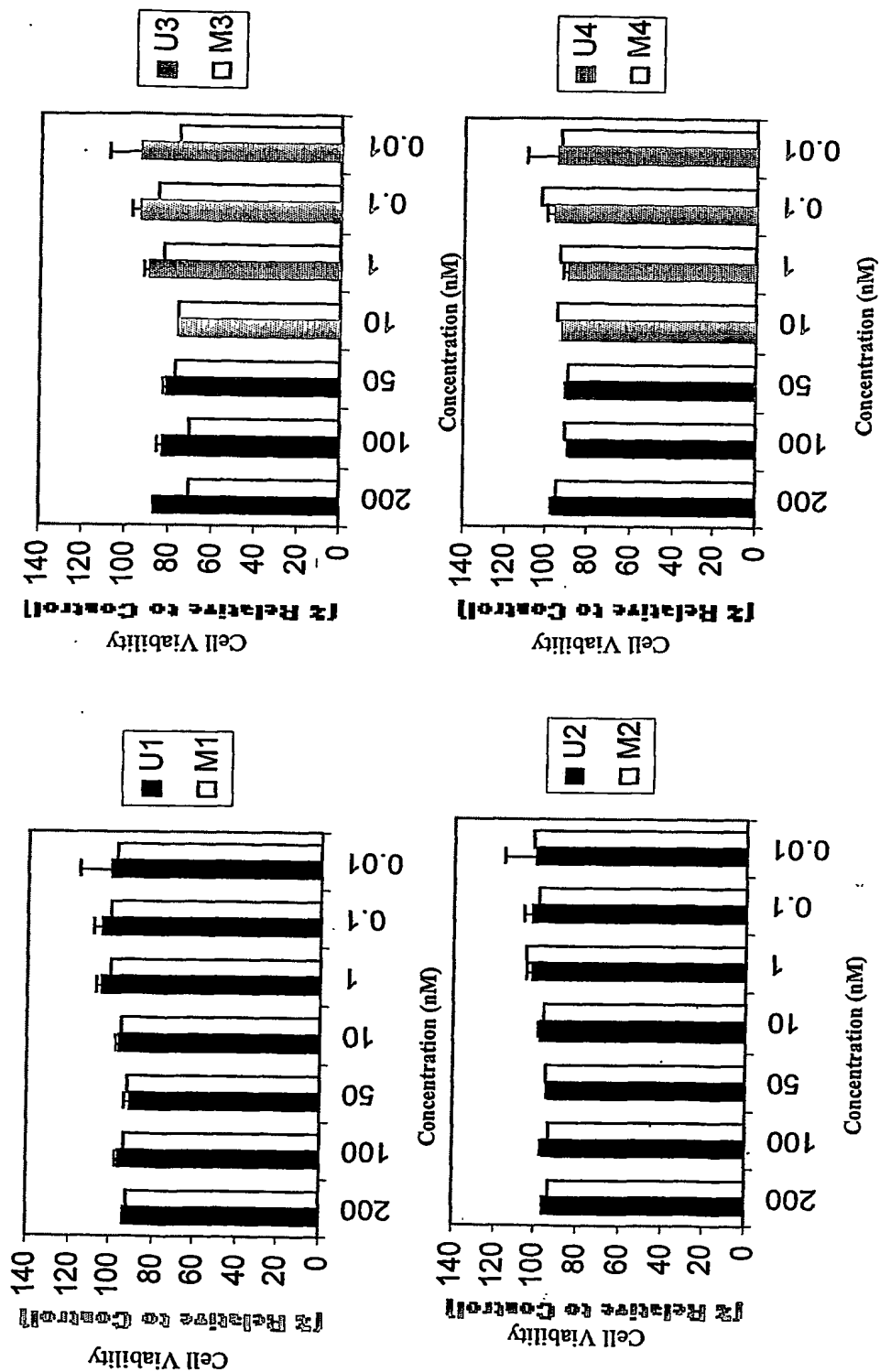
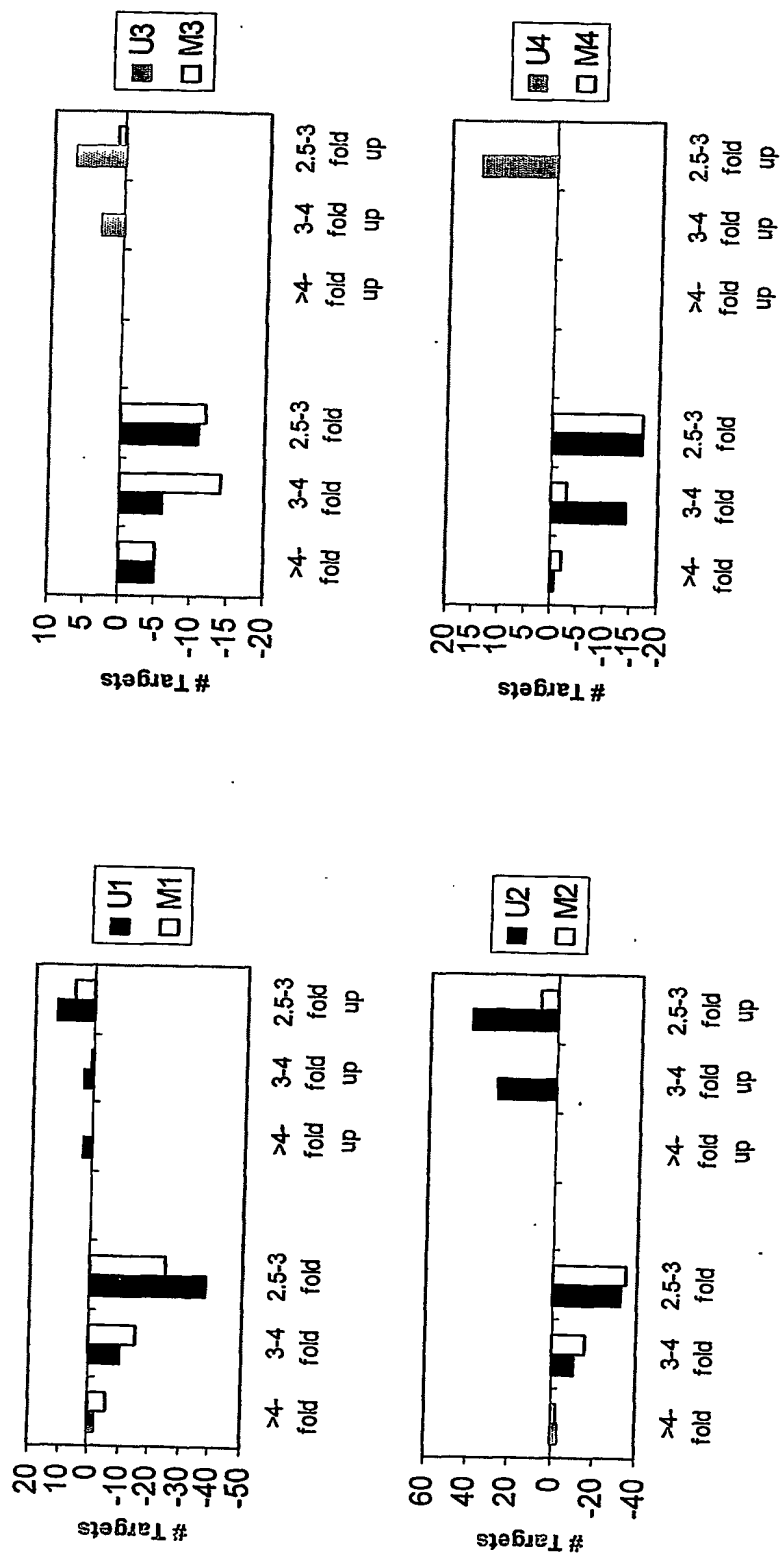


Figure 40





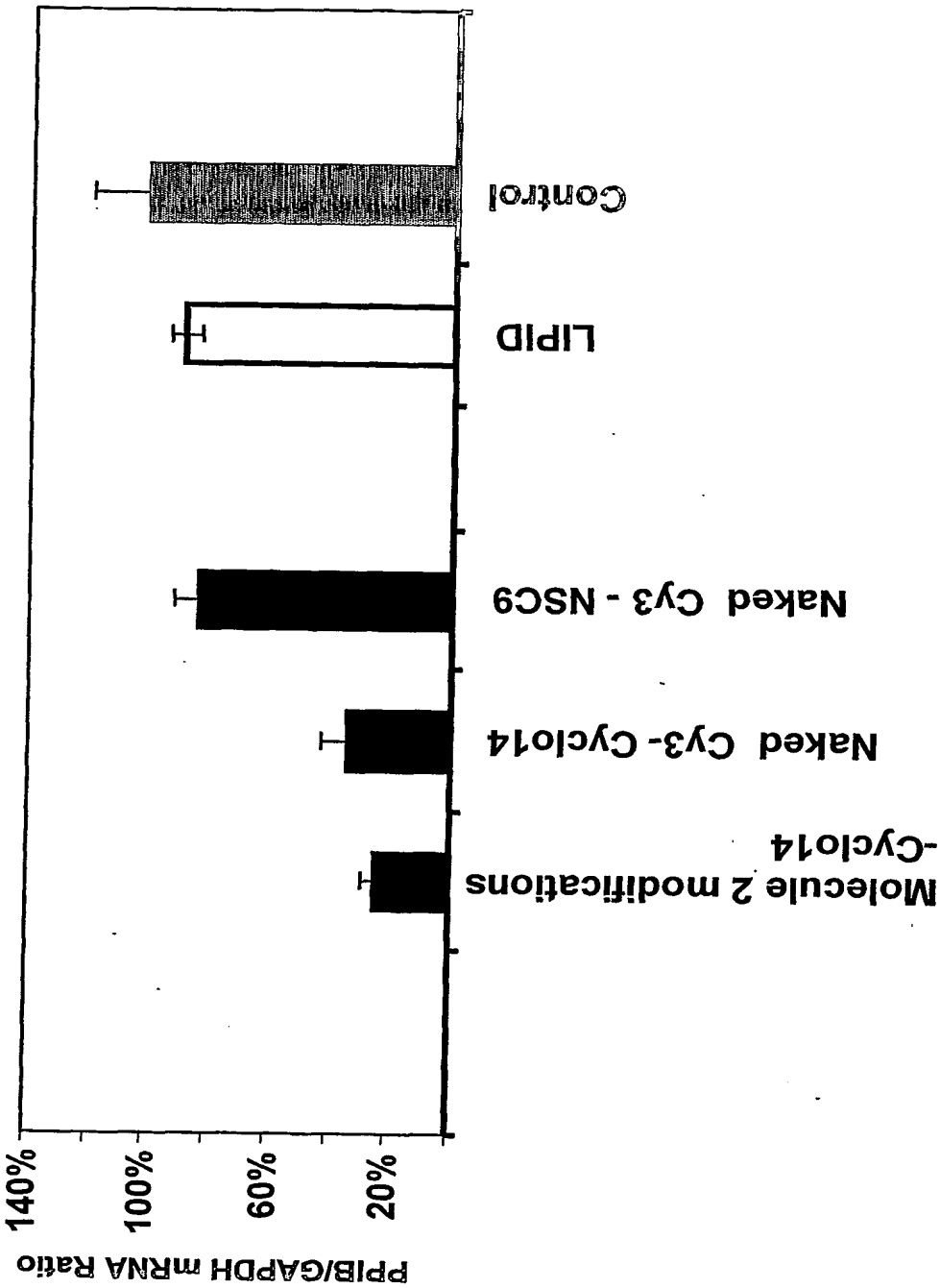
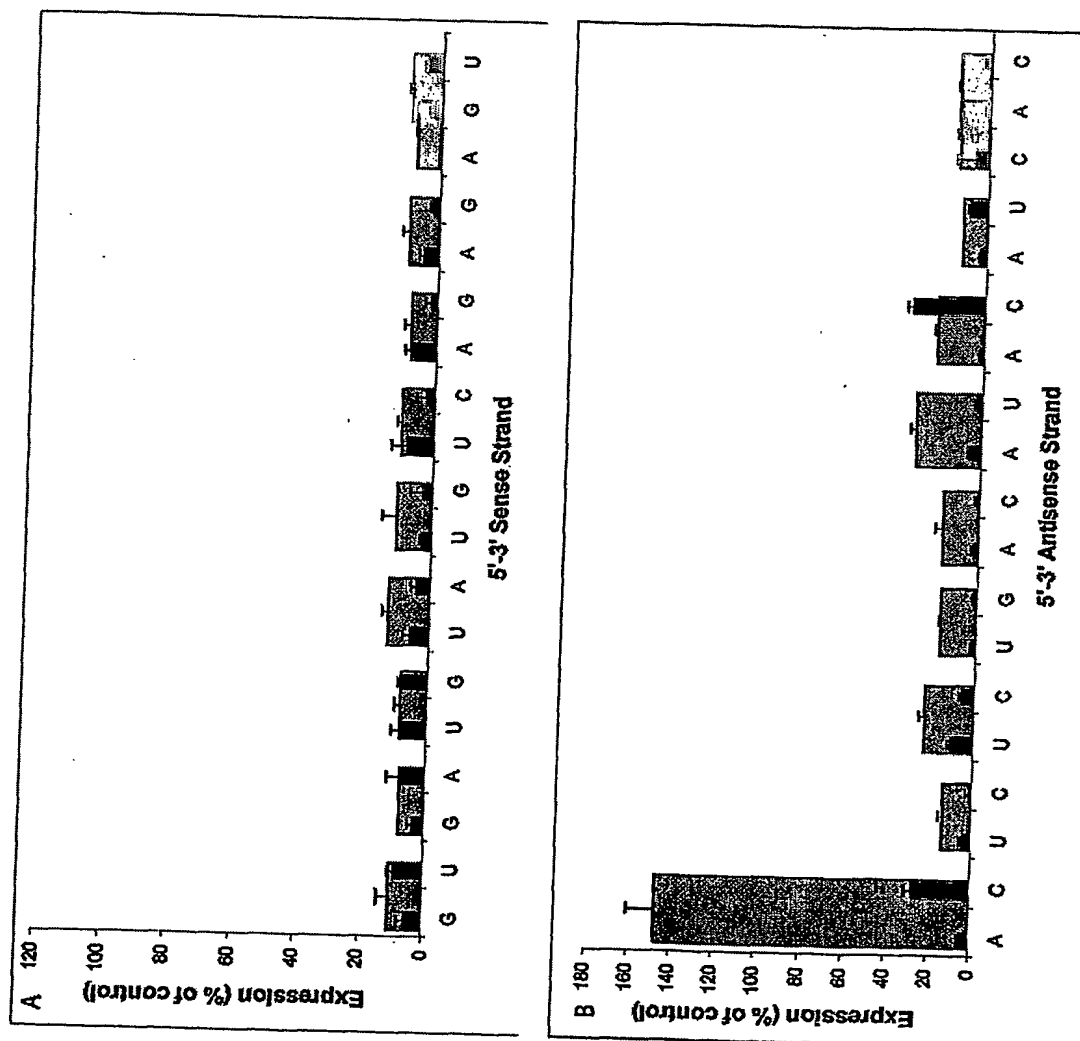


Figure 42



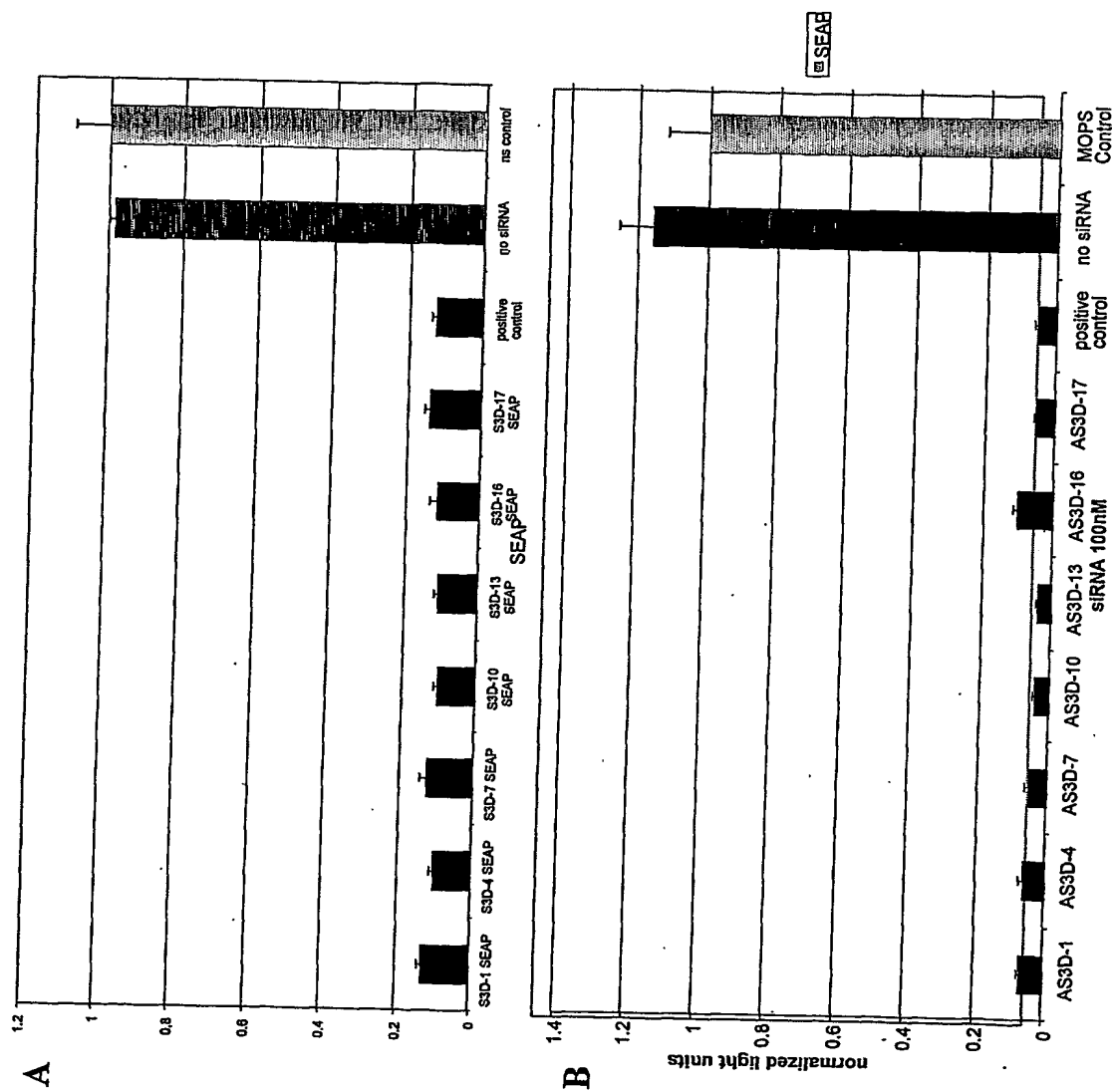
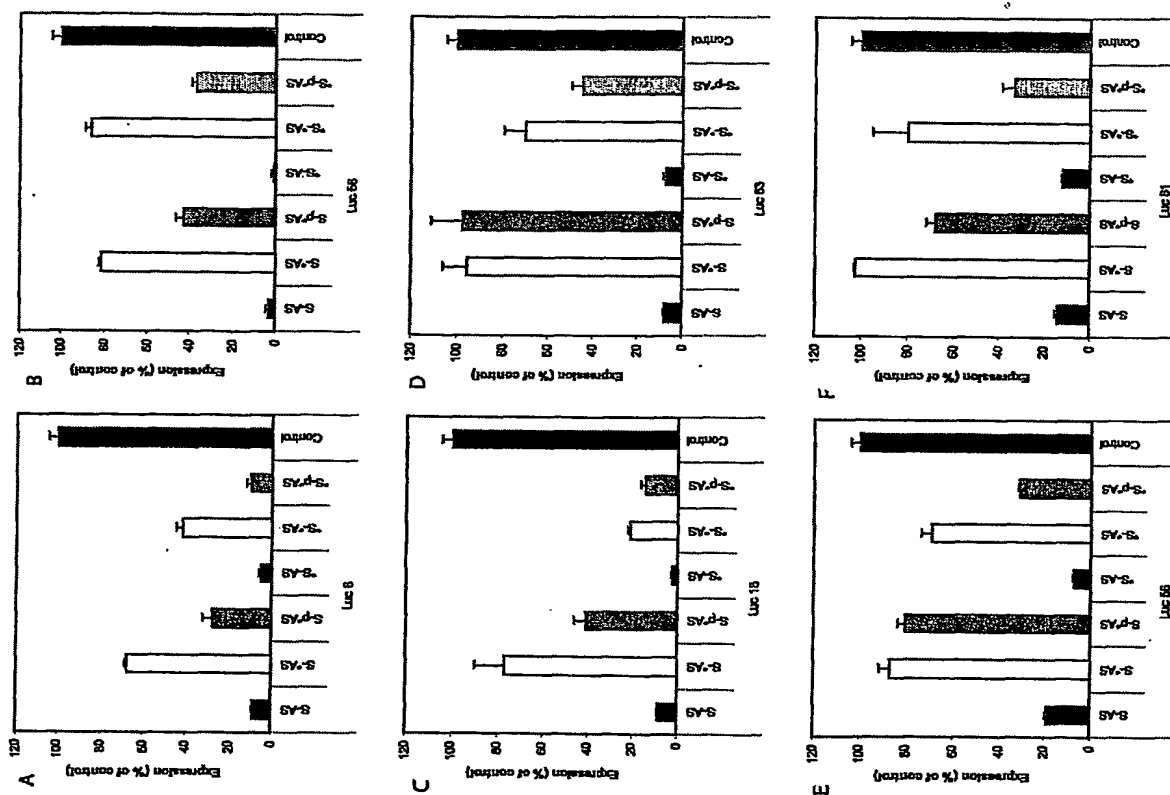
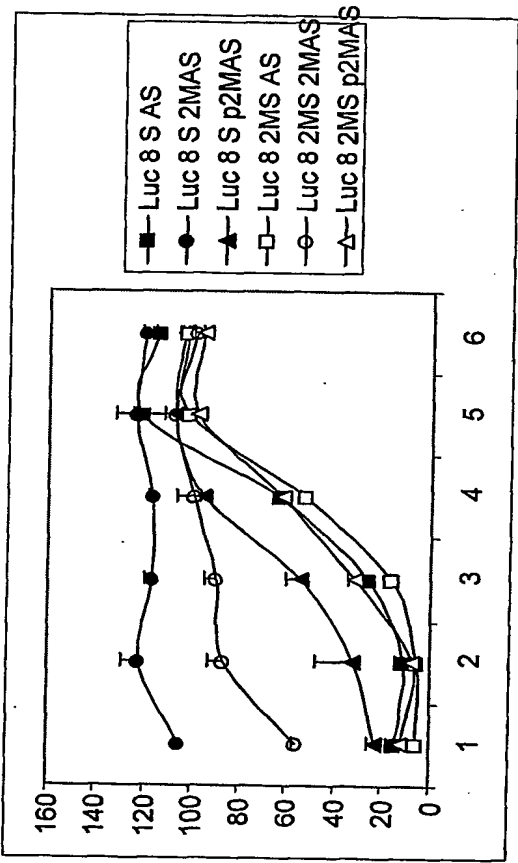


Figure 44



## Figure 45

46A



46B

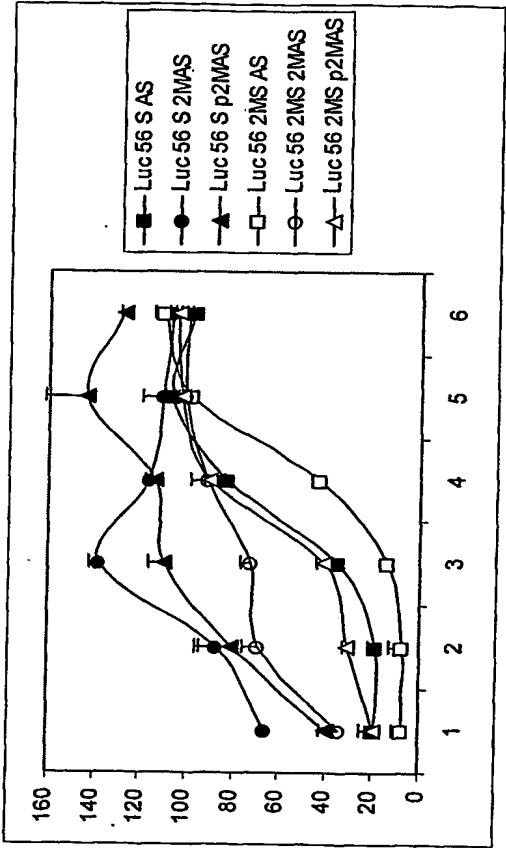


Figure 46A,B

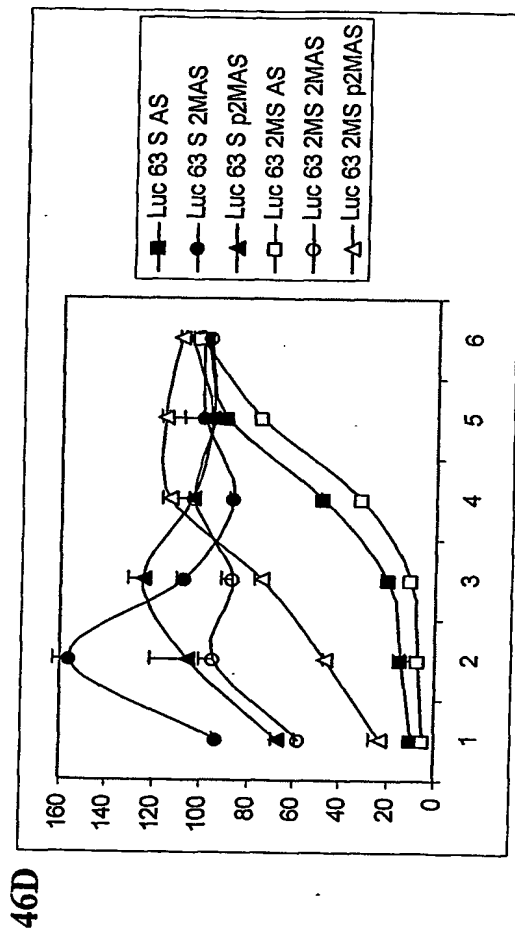
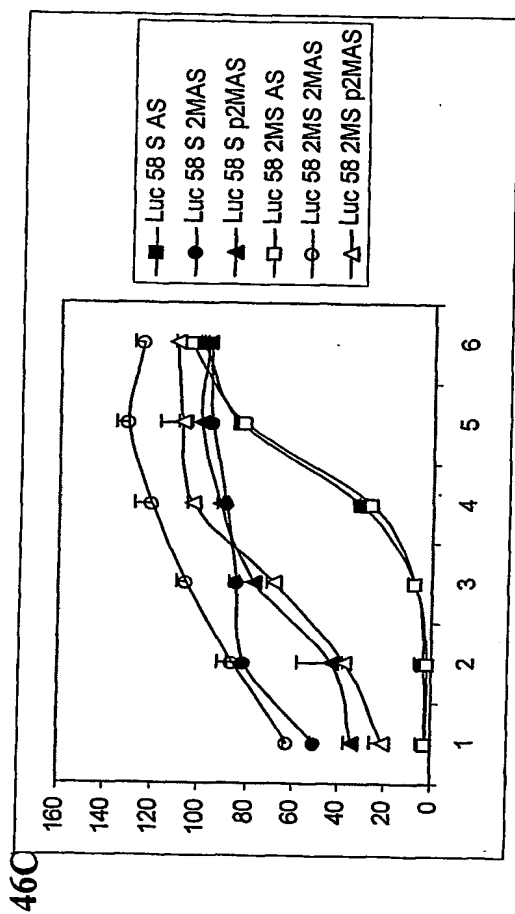


Figure 46C,D

46E

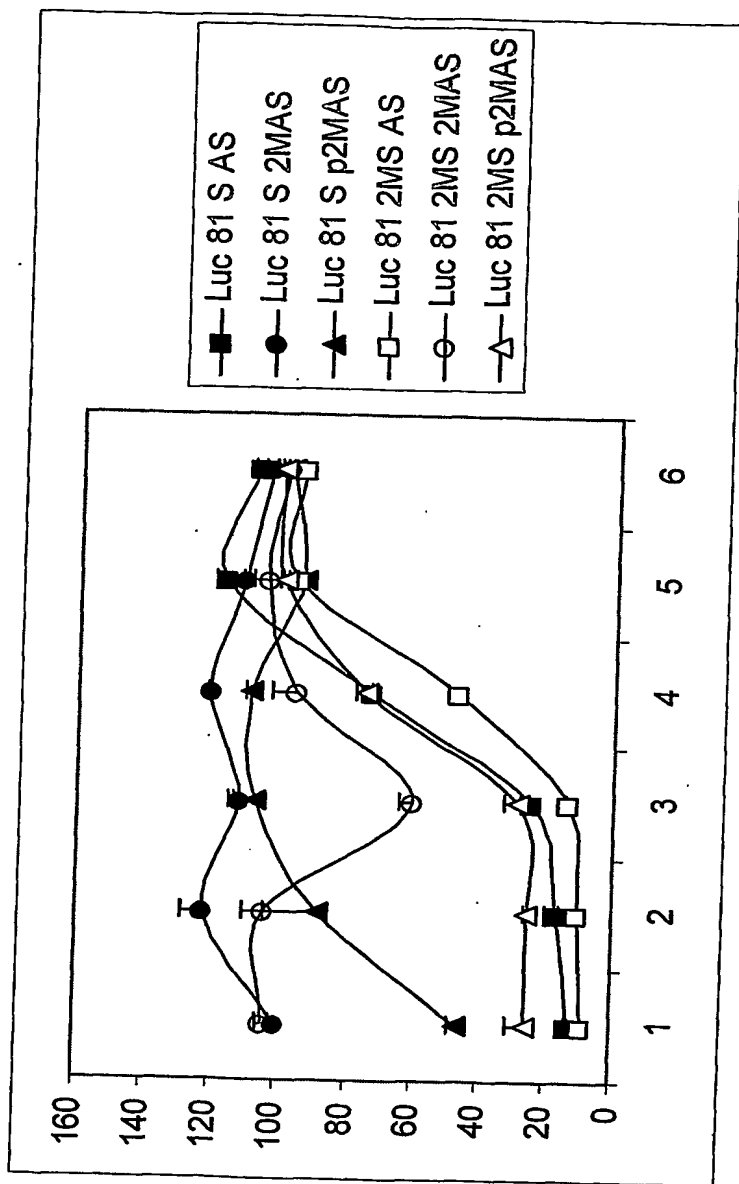
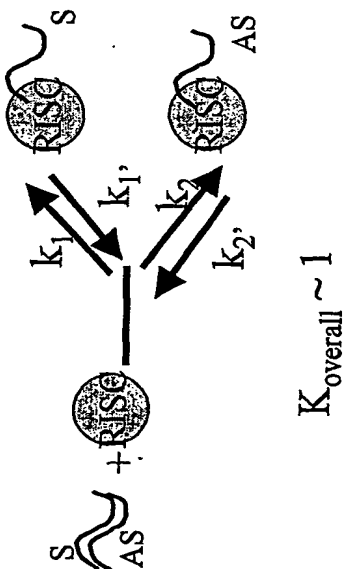
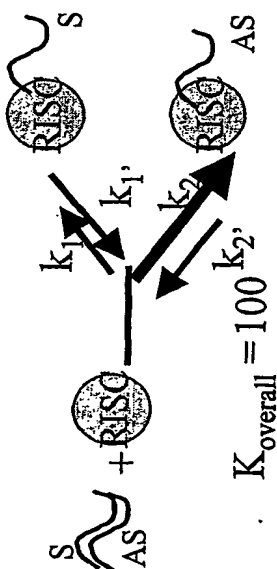
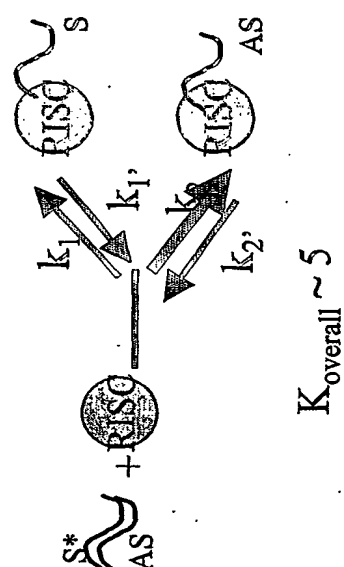
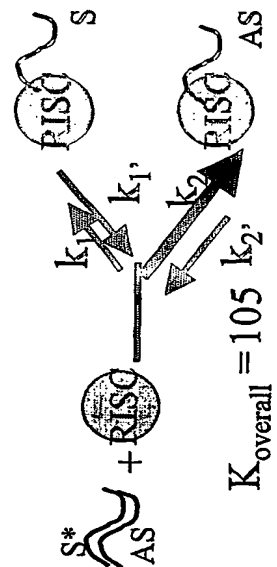
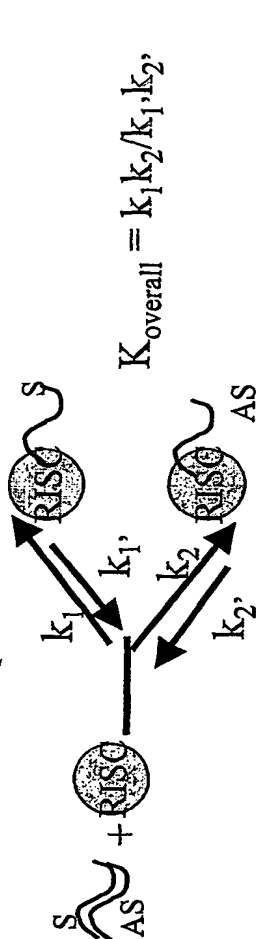


Figure 46E



**Figure 47**



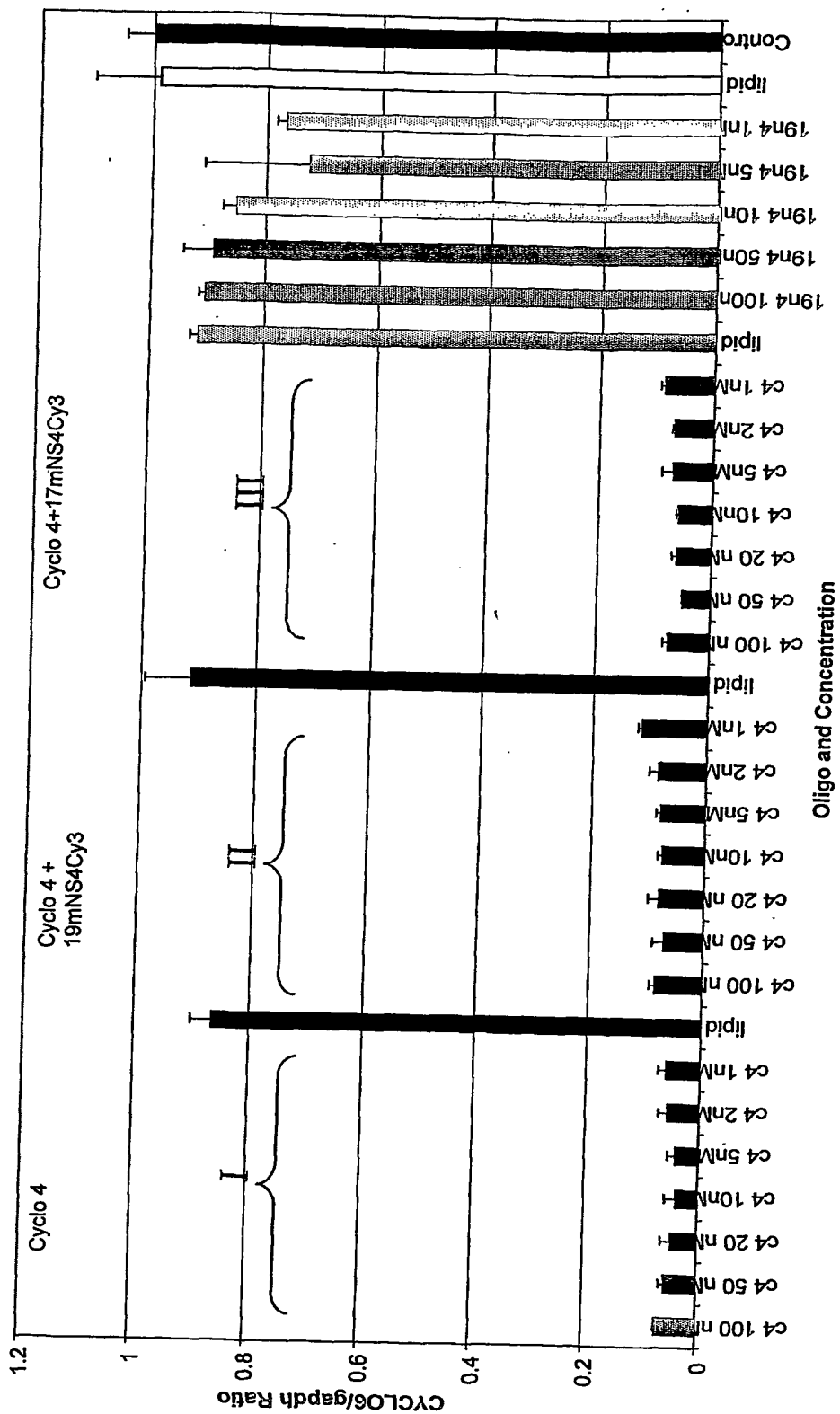


Figure 48A

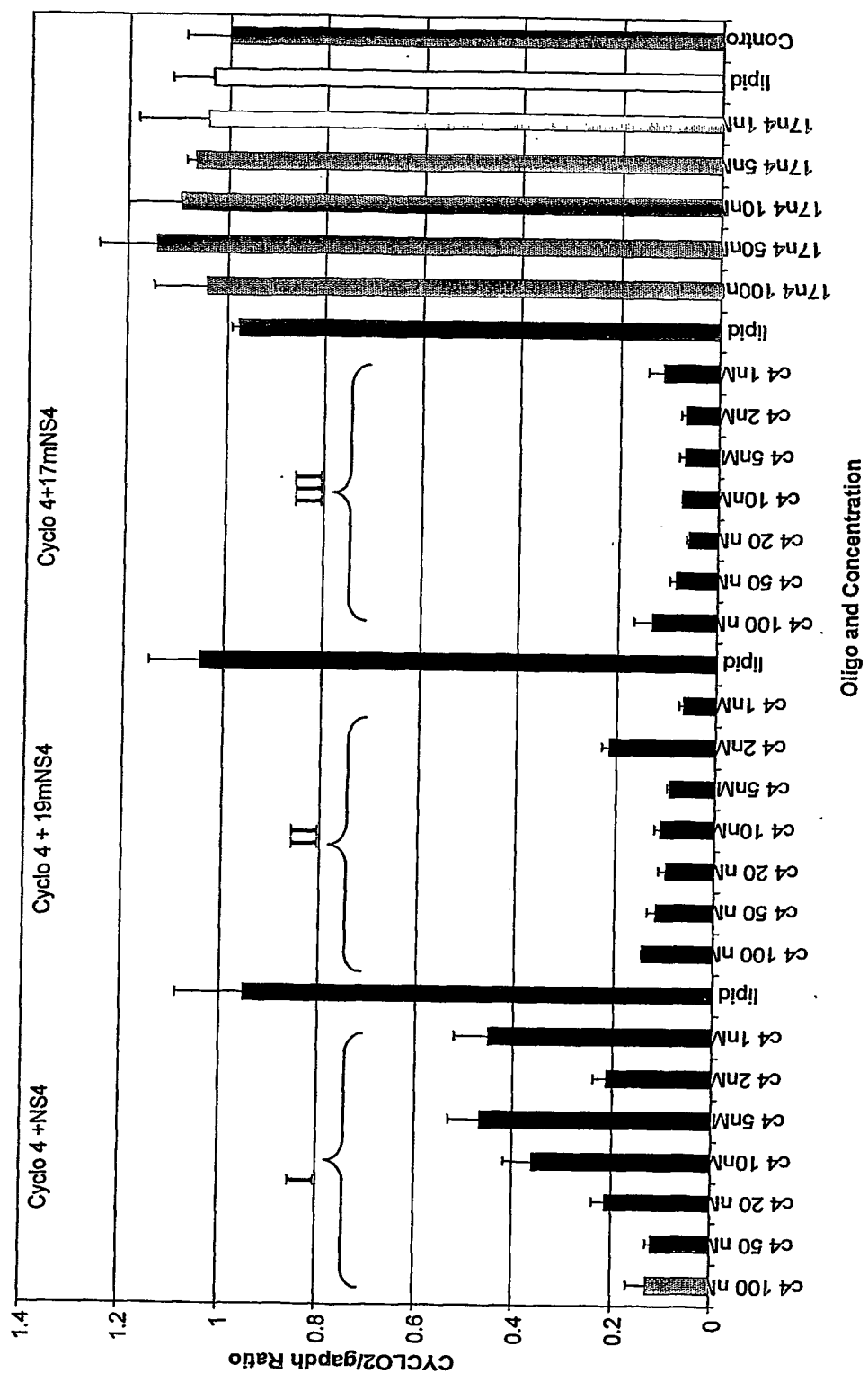


Figure 48B

GAPDH 4 competition assay

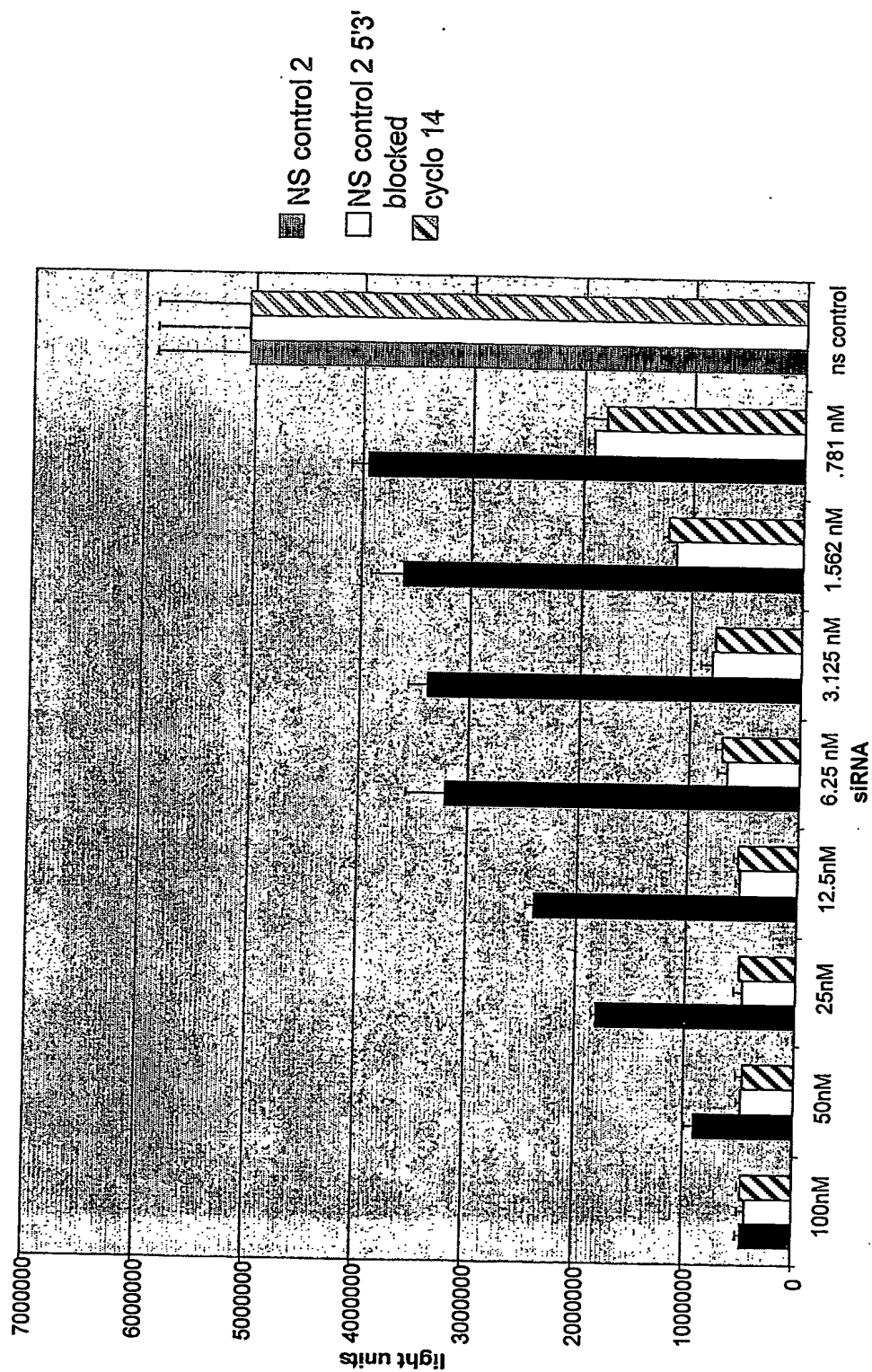


Figure 49

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